Academy of Medicine,
Singapore

Autism Spectrum Disorders in Pre-School Children

AMS-MOH Clinical Practice Guidelines 1/2010

College of Family Physicians,
Singapore

College of Paediatrics and Child Health,
Singapore

MINISTRY OF HEALTH
SINGAPORE

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Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Autism Spectrum Disorders in Pre-School Children

AMS-MOH Clinical Practice Guidelines 1/2010

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Autism spectrum disorders (ASD) are a group of developmental disorders characterised by impaired communication and social interaction, restricted interests and repetitive behaviours, with onset before 3 years of age. Examples of ASD include Autism and Asperger syndrome. Although the degree of severity and impairment in ASD is highly variable, ASD have a profound impact on the affected children and their families.

Current estimates of global prevalence of ASD range between 50 to 60 per 10,000 school-aged children, making ASD a serious public health concern.[i] Locally, the Singapore Burden of Disease Study 2004 found ASD to be the leading cause of disease burden in children aged between 0-14 years, causing a loss of more than 5110 disability-adjusted life years (DALYs) in 2004 (20.7% of total DALYs lost in this age group).[ii]

There is significant variance in the assessment practices and diagnostic criteria used by healthcare professionals who work with children with ASD. Furthermore, an increasing number of parents and caregivers of children with ASD are turning to complementary and alternative therapies publicised in the media; these therapies might not have a strong scientific basis and might be ineffective or even harmful to the children.

It is therefore timely to develop this first national guideline that incorporates the best available evidence from the scientific literature to assist all children with ASD and the healthcare professionals who work with them.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

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[i] Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health. 2007;28:235-58.

[ii] Ministry of Health, Singapore. Singapore burden of disease study 2004. [Online]. 2009 Mar 1 [cited 2010 Mar 2]. Available from: URL: http://www.moh.gov.sg/mohcorp/publicationsreports.aspx?id=23040

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

"ASD" refers to "autism spectrum disorders". Please refer to pages 19-20 for a detailed definition.

Definition and diagnostic classification

C All professionals involved in diagnosing ASD in children should consider using either the ICD-10 or DSM-IV-TR systems of classification (pg 20).

Grade C, Level 2+

Surveillance

D Professionals should aim to identify ASD early. Early identification provides opportunity for early referral and intervention, so that the child with ASD may have improved functioning in later life (pg 21).

Grade D, Level 3

GPP Parents' or caregivers' attention should be drawn to the parental checklist(s) in the Health Booklet (provided to parents at the child's birth) that describes normal development in children. Parents should be encouraged to inform their healthcare professional if they suspect delay or abnormality in their child's development or behaviour (pg 21).

GPP

C Parental or caregiver concerns about communication, interaction and play skills as well as behaviour should be elicited in a general developmental surveillance programme. Healthcare professionals should be aware that parental or caregiver concerns regarding delayed or deviant development are as important as clinically abnormal or atypical features (pg 21).

Grade C, Level 2+

D All professionals who deal with pre-school children, whether in health care services or early childhood education centres, should receive training on the "key signs" that suggest a diagnosis of ASD (pg 22).

Grade D, Level 4

D Active surveillance by healthcare professionals is recommended at 18 months and again at 24-36 months for key signs of ASD (pg 22).

Grade D, Level 3

D Children with one or more of the following clinical features must be referred promptly for comprehensive developmental evaluation:

1) No babble, pointing or other gesture by 12 months,
2) No single words by 18 months,
3) No spontaneous (non-echoed) 2-word phrases by 24 months,
4) Any loss of language or social skills at any age.

(pg 23) **Grade D, Level 4**

Screening

C In the general population, screening for ASD is not recommended (pg 24).

Grade C, Level 2++

C In a high-risk population, screening for ASD is highly recommended (pg 25).

Grade C, Level 2+

Assessment

D Diagnostic evaluation of a child suspected to have ASD should be carried out by a multi-disciplinary team or professional who is trained and experienced with diagnosis of ASD. Evaluation includes:

a) an ASD-specific developmental history,
b) direct observations,
c) obtaining wider contextual and functional information.

In addition, the pre-school child with ASD should undergo thorough clinical and neurological examination to exclude associated medical conditions (pg 27).

Grade D, Level 4

C ASD-specific instruments should be considered when taking a developmental history as it increases the reliability of an ASD diagnosis (pg 27).

Grade C, Level 2+

D Professionals should conduct direct observations of the child's social and communication skills as well as behaviours (pg 28).

Grade D, Level 4

GPP Information about a child's functioning in relevant community and educational settings should be routinely obtained either through direct observations or interviews with relevant persons (pg 28).

GPP

C ASD-specific observational instruments should be used to increase the reliability of diagnosis (pg 28).

Grade C, Level 2+

Prognosis

GPP In children diagnosed with ASD before three years old, parents should be advised that it is difficult to reliably predict prognosis, because individual outcomes are extremely variable and depend on many factors (pg 29).

GPP

Aetiology

C Parents of children with ASD may require genetic counselling regarding the risk of recurrence of ASD in the next pregnancy (pg 32).

Grade C, Level 2+

B Parents should be educated to proceed with their child's vaccination schedule, including the MMR vaccine (pg 34).

Grade B, Level 2+

B Parents should be reassured that ASD is not associated with thimerosal-containing vaccines (pg 34).

Grade B, Level 2+

Investigations

D The pre-school child with ASD may require specific medical investigations based on history and clinical examination (pg 35).

Grade D, Level 4

C Children with ASD should have a complete audiologic assessment to obtain comprehensive information on their hearing status including middle ear function (pg 35).

Grade C, Level 2+

C Where the hearing status of a child cannot be determined by age-appropriate behavioural audiometry, electro-physiological tests such as oto-acoustic emissions, auditory brain-stem response or auditory steady-state response is recommended to at least provide good estimates of hearing thresholds (pg 36).

Grade C, Level 2+

D Children with ASD with the following features should have a genetic evaluation:

a) microcephaly or macrocephaly
b) a positive family history (of a genetic syndrome)
c) dysmorphic features.

(pg 36)

Grade D, Level 3

D Children with ASD may be offered high-resolution chromosomal studies and DNA analysis to look for an associated medical condition following diagnosis (pg 37).

Grade D, Level 3

C Children with ASD may be offered selective metabolic testing when an inborn error of metabolism is suspected (pg 37).

Grade C, Level 2+

C Brain imaging is not routinely recommended in children with ASD (pg 37).

Grade C, Level 2+

C Electro-encephalography (EEG) is not routinely recommended in children with ASD but should be considered if any of the following are present:

a) clinical seizures
b) symptoms suggestive of sub-clinical seizures such as staring spells
c) a history of developmental regression.

(pg 38) **Grade C, Level 2+**

D Serum lead screening is not routinely indicated in children with ASD but may be considered where there is clinical suspicion of pica (pg 38).

Grade D, Level 4

C Food allergy tests are not recommended in the routine assessment of children with ASD (pg 38).

Grade C, Level 2+

C Hair mineral analysis is not recommended in the evaluation of children with ASD (pg 39).

Grade C, Level 2+

C Immunologic investigation is not routinely indicated in children with ASD (pg 39).

Grade C, Level 2+

C Assay of vitamin B6 and magnesium levels is not recommended in children with ASD (pg 39).

Grade C, Level 2+

C Investigations to identify yeast over-growth in the gastro-intestinal tract are not recommended in children with ASD (pg 39).

Grade C, Level 2+

Management: Intervention

D Every pre-school child diagnosed with ASD should have an individualised intervention plan that sets out the goals, type(s), frequency and intensity of intervention, in order to address particular developmental and educational needs (pg 41).

Grade D, Level 4

D An individualised intervention plan should consist of a variety of quality programmes and activities. This includes attendance in comprehensive early intervention programmes, programmes targeting specific needs and also positive engagement with parents and/or caregivers (pg 41).

Grade D, Level 4

C All pre-school children with ASD should undergo early intervention as soon as significant developmental need is recognized by a trained professional because outcomes improve with early intervention (pg 41).

Grade C, Level 2++

D The intensity of intervention should be continually monitored and varied according to the child's changing need (pg 42).

Grade D, Level 4

D Interventions for impaired communication should address the development of pivotal skills such as spontaneity, initiation, motivation and self-regulation (pg 43).

Grade D, Level 4

A Interventions for impaired communication should aim to increase joint attention and symbolic play in order to improve expressive language development (pg 43).

Grade A, Level 1+

D There is no single language or communication intervention method that is appropriate for all children with ASD. The optimal communication intervention for an individual child with ASD depends on the needs of that particular child (pg 44).

Grade D, Level 4

A Alternative-augmentative communication systems may be recommended for pre-school children with ASD because they expand (spoken or written) communication, may stimulate speech acquisition in non-verbal children and enhance expression in verbal children (pg 44).

Grade A , Level 1+

A Visual strategies are useful interventions for children with ASD because they offer visual support to communication, increase spontaneous imitation and socially communicative behaviour (pg 45).

Grade A, Level 1+

D Parent/caregivers should be educated that the use of alternative-augmentative communication systems or visual strategies neither inhibits speech nor replaces the development of expressive spoken language skills (pg 45).

Grade D, Level 4

D Social skills are best taught explicitly through modeling and feedback (pg 45).

Grade D, Level 3

D Social skills programmes depend on the functioning level of the preschool child with ASD and may include

- Assessment and teaching of social skills interaction in natural settings
- Provision of structure, visual cues and predictability
- Making abstract concepts more "concrete".
- Activities that enable purposeful and appropriate interaction with typically developing peers.
- Goals focusing on fostering self-appreciation and self esteem.

(pg 47)

Grade D, Level 4

B Interventions for children with ASD with challenging behaviours based on functional behavioural assessment are recommended (pg 47).

Grade B, Level 1+

B Children with ASD who present with perceptual distortions, fine and gross motor co-ordination difficulties, impaired play skills and impaired self-care and adaptability may benefit from consultation with appropriate specialists such as occupational therapists and/or physiotherapists (pg 48).

Grade B, Level 2+

GPP In the assessment and management of feeding difficulties in children with ASD, the healthcare professional needs to consider challenges in executive functioning, fears, sensory processing, social and language skills (pg 49).

GPP

D Management of gastro-intestinal disorders and feeding difficulties in children with ASD may require collaboration between healthcare professionals such as primary care doctors, paediatricians, gastro-enterologists, dietitians and therapists (pg 49).

Grade D, Level 4

D Environment, tasks and timing of activities of children with ASD should be adapted to minimize negative sensory reactions and meet their sensory needs (pg 50).

Grade D, Level 4

D "Sensory integration" intervention is not recommended as standard therapy in management of children with ASD but may be considered where the child has sensory difficulties that affect daily functioning (pg 50).

Grade D, Level 3

A Early Intensive Behavior Intervention (EIBI) can be recommended as an intervention option for children with ASD (pg 51).

Grade A, Level 1++

C Structured Teaching can be recommended as an intervention option for children with ASD (pg 51).

Grade C, Level 2+

D The Hanen "More Than Words®" programme may be considered as an intervention option for children with ASD (pg 52).

Grade D, Level 3

D Developmental models such as Developmental, Individual-difference, Relationship-based (DIR)/Floortime and Relationship Development Intervention (RDI) models may be considered as intervention options for children with ASD (pg 52).

Grade D, Level 3

Management: Family and caregiver support

D Parents and caregivers should be encouraged to discuss the need for practical emotional support. This enables information to be provided, referrals made and support services made available (pg 53).

Grade D, Level 3

A Parents and caregivers of pre-school children with ASD are recommended to attend parent education programmes (pg 54).

Grade A, Level 1+

GPP Parents and caregivers are recommended to consult appropriate professionals when considering educational placement for their child with ASD, e.g. child and educational psychologists who are informed of the special educational provisions in Singapore (pg 55).

GPP

D Parents and caregivers are recommended to actively collaborate with professionals and teachers in preparing the child with ASD for the new educational setting, as well as modifying the new setting to accommodate the needs of the child (pg 55).

Grade D, Level 4

GPP Parents and caregivers should be encouraged to give consent for information about special educational needs to be shared with school personnel for better planning of intervention and support (pg 55).

GPP

Management: Pharmacological treatment

D Pre-school children with ASD are best managed by a multi-modal approach (pg 56).

Grade D, Level 4

D Pharmacological treatment does not cure ASD. It may be considered when specific indications are present, such as aggressive and self-injurious behaviour, anxiety, depression, tics, obsessive-compulsive behaviours, hyperactivity and sleep disturbances (pg 56).

Grade D, Level 4

D Pharmacological treatment should be given by doctors with appropriate training in mental health (pg 56).

Grade D, Level 4

B Clomipramine may be considered for reducing irritability and stereotypical behaviour in children with ASD. Monitoring for tolerance and side-effects to clomipramine is recommended (pg 58).

Grade B, Level 1+

D Fluvoxamine may be considered for repetitive thought and maladaptive behaviour but should be used with caution in children with ASD because of limited efficacy and poor tolerance (pg 59).

Grade D, Level 3

B Fluoxetine may be considered for the reduction of repetitive behaviours in children and adolescents with ASD. Monitoring for the side effects of fluoxetine is recommended (pg 59).

Grade B, Level 1+

B Haloperidol may be considered in the management of temper tantrums, aggression, hyperactivity, withdrawal and stereotypical behaviour in children with ASD, but careful monitoring of side effects is required (pg 60).

Grade B, Level 1+

A Atypical (second-generation) anti-psychotic medications are associated with potentially adverse metabolic effects, such as weight gain, insulin resistance, dyslipidaemia and hyperglycemia. Taking a thorough medical history and monitoring of body weight and blood sugar levels is recommended when atypical anti-psychotic medications are administered (pg 60).

Grade A, Level 1++

A Risperidone is recommended for the management of irritability, hyperactivity and stereotypic behaviour when used as short term treatment for children with ASD (pg 61).

Grade A, Level 1++

D Olanzapine may be considered in the management of motor restlessness, self-injurious behaviour, aggression and irritability in children with ASD (pg 61).

Grade D, Level 3

A Olanzapine administered to children with ASD may result in significant weight gain and healthcare professionals should monitor the child's weight closely (pg 61).

Grade A, Level 1+

A Methylphenidate may be considered for treating hyperactivity in children with ASD, although the magnitude of response is often less than that seen in typically developing children with attention deficit hyperactivity disorder (pg 62).

Grade A, Level 1++

GPP Pre-school children with ASD receiving methylphenidate should be monitored for adverse effects (pg 63).

GPP

D Atomoxetine may be considered for managing attention deficit hyperactivity disorder-like symptoms in children with ASD (pg 64).

Grade D, Level 3

B Melatonin may be considered in the management of the disturbed sleep patterns of children with ASD (pg 64).

Grade B, Level 1+

Management: Complementary alternative therapies

GPP Parents and caregivers should not replace mainstream interventions for pre-school children with ASD with complementary and alternative therapies (pg 65).

GPP

GPP Healthcare professionals caring for pre-school children with ASD should advise and counsel parents and caregivers about relevant, safe and effective health services and therapies regardless of whether the therapies are mainstream or complementary alternative therapies (pg 66).

GPP

The following complementary alternative therapies are **not recommended** for pre-school children with ASD because of insufficient, conflicting or inconclusive evidence:

- Amino acid supplementation
- Animal-assisted therapy
- Behavioural optometry
- Expressive psychotherapy
- Gluten-free and/or casein-free diet
- Sound therapies (Samonas Sound Therapy and the Listening Programme)
- Massage and other sensory-based interventions
- Music therapy
- Omega-3 fatty acid (O3FA) supplementation

D High dose amino acid supplementation is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy (pg 67).

Grade D, Level 3

D Animal-assisted therapy is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy (pg 67).

Grade D, Level 3

D Behavioural optometry is not recommended in the routine management of children with ASD because of conflicting evidence (pg 68).

Grade D, Level 3

D Expressive psychotherapy is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy (pg 68).

Grade D, Level 3

D Gluten-free casein-free diets are not recommended in the routine management of children with ASD because of conflicting evidence (pg 69).

Grade D, Level 3

D Sound therapies (either as Samonas or the Listening Programme®) are not recommended in the routine management of children with ASD because of insufficient evidence for efficacy (pg 70).

Grade D, Level 3

D Massage and other sensory-based interventions are not recommended in the routine management of children with ASD because of insufficient evidence for efficacy (pg 70).

Grade D, Level 3

D Music therapy is not recommended in the routine management of children with ASD because of inconclusive evidence (pp 71).

Grade D, Level 3

D High dose omega-3 fatty acid supplementation is not recommended in the routine management of children with ASD because of inconclusive evidence for efficacy (pg 71).

Grade D, Level 3

The following complementary alternative therapies are **not recommended** in the routine management of children with ASD because of evidence that they are ineffective:

- Dimethylglycine supplementation
- Patterning therapy without masking

D Dimethylglycine supplementation is not recommended for pre-school children with ASD because it is ineffective (pg 72).

Grade D, Level 3

D Patterning without masking is not recommended for pre-school children with ASD because it is ineffective (pg 73).

Grade D, Level 4

The following complementary alternative therapies are **not recommended** in pre-school children with ASD because of potential for harm or adverse effects:

- Acupuncture
- Antibiotics and Anti-yeast medication
- Ascorbic acid (vitamin C) supplementation
- Auditory Integration Therapy
- Chelation therapy
- Chiropractic
- Cranio-sacral therapy
- Digestive enzymes
- Facilitated Communication
- Folate supplementation
- Holding Therapy
- Hyperbaric Oxygen Therapy
- Intravenous Immunoglobulin therapy
- Patterning with masking
- Secretin therapy
- Vitamin B6-Magnesium supplementation
- Weighted vests
- Zinc supplementation

D Acupuncture is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for harm† (pg 74).

***†Grade D, Level 3**

D Antibiotic and anti-yeast therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for adverse effects† (pg 75).

***†Grade D, Level 3**

D High dose ascorbic acid supplementation is not recommended for ASD because of insufficient evidence for efficacy* and the potential for adverse effects† (pg 75).

***Grade D, Level 3**
†Grade D, Level 4

A&D Auditory Integration Therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for damage to hearing† (pg 76).

***Grade A, Level 1++**
†Grade D, Level 3

D Chelation therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for harm including death† (pg 76).

***†Grade D, Level 3**

D Chiropractic is not recommended for children with ASD because of conflicting evidence of efficacy* and the potential for harm† (pg 77).

***†Grade D, Level 3**

D Cranio-sacral therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for harm† (pg 77).

***Grade D, Level 3**
†Grade D, Level 4

D Digestive enzyme therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for adverse effects† (pg 78).

***Grade D, Level 3**
†Grade D, Level 4

A&D Facilitated communication is not recommended for children with ASD because of lack of efficacy* and the potential for abuse†(pg 78).

***Grade A, Level 1+**
†Grade D, Level 3

D High dose folate supplementation is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for adverse effects† (pg 79).

***Grade D, Level 3**
†Grade D, Level 4

D Holding therapy is not recommended for children with ASD because of lack of efficacy* and the potential for harm, including death† (pg 79).

***†Grade D, Level 3**

D Hyperbaric oxygen therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for harm† (pg 80).

***Grade D, Level 3**
†Grade D, Level 4

D Immunoglobulin therapy is not recommended for children with ASD because it is ineffective* and there is potential for adverse effects† (pg 80).

***†Grade D, Level 3**

D Patterning with Masking is not recommended for children with ASD because it is ineffective* and there is potential for harm to the child's developing brain† (pg 81).

***†Grade D, Level 4**

A&D Intravenous secretin is not recommended for children with ASD because it is ineffective* and there is potential for serious adverse effects† (pg 81).

***Grade A, Level 1++**
†Grade D, Level 4

D High dose vitamin B6-magnesium supplementation is not recommended for children with ASD because of conflicting evidence* and the potential for adverse effects† (pg 82).

***Grade D, Level 3**
†Grade D, Level 4

D Wearing of weighted vests is not recommended for children with ASD because of insufficient evidence of efficacy* and potentially adverse effects on the developing spine† (pg 82).

***Grade D, Level 3**
†Grade D, Level 4

D Zinc supplementation is not recommended for children with ASD because of insufficient evidence for efficacy* and potential for adverse effects† (pg 82).

***†Grade D, Level 4**

1 Introduction

1.1 Background information

Autism Spectrum Disorders (ASD) are developmental disorders increasingly recognised as being more common than previously considered. The present worldwide prevalence ranges from 50-60 per 10,000 school-aged children compared to 2-4 per 10,000 children in the 1980s. Whilst prevalence rates are unavailable in Singapore, there are at least 400 new cases diagnosed annually at the Department of Child Development, KK Hospital (KKH) and Child Development Unit, National University Hospital (NUH).

Professionals involved are well aware of the importance of accurate diagnosis and early intervention. Increased public awareness coupled with higher expectations for services in the area of early identification and intervention has provided impetus for the formulation of this clinical practice guideline (CPG).

1.2 Objectives and scope of guideline

Accurate diagnosis of ASD can be difficult. Multi-disciplinary and multi-agency involvement contributes to complexity of diagnosis and management. The purpose of this CPG is to "localise" guidelines for usage within the Singapore context. This is because existing guidelines produced by other countries are not always applicable locally. These guidelines are formulated to assist practitioners who are involved in any of the following: surveillance, screening and early identification, referral for assessment, diagnosis and intervention of children with ASD.

The uncertainty in screening and diagnostic processes, controversy over pharmacological treatment, early intervention and efficacy of complementary alternative therapy are addressed in this CPG. This CPG was prepared for use as a guideline (not protocol) and intervention for any particular child with ASD must be individualised.

1.3 Target group

Most children in Singapore attend primary schools beginning the year that they turn 7. This CPG is prepared for all professionals who are in contact with pre-school children up to the age of 8 years. It is applicable to those who may have started pre-school late or been retained at pre-school. Professionals should exercise due caution when extrapolating the guidelines to other populations beyond pre-school, e.g. school-going children or adults. The guidelines would benefit healthcare professionals (primary care doctors, paediatricians, psychiatrists, nurses, psychologists, therapists, dieticians), social workers, early childhood educators, parents and community groups supporting children with ASD.

1.4 Guideline development

These guidelines were produced by a multi-disciplinary workgroup appointed by the Academy of Medicine, Singapore. The workgroup committee comprised developmental paediatricians, primary care doctors, psychiatrists, psychologists, occupational therapists, speech and language therapists, dieticians and special educators from restructured hospitals, private sector, Ministry of Education and the Early Intervention Programmes under the purview of the National Council of Social Services.

The workgroup on ASD covered the following:

- Definition and Diagnostic Classification
- Surveillance, Screening, Assessment and Prognosis
- Aetiology and Investigations
- Early Intervention
- Family and Caregiver Support
- Pharmacological Treatment
- Complementary Alternative Therapies

1.5 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or earlier if new evidence appears that requires substantive changes to the recommendations.

2 Definition and diagnostic classification

The term "autism spectrum disorders" (ASD) reflects the broad spectrum of clinical characteristics that encompass complex developmental disorders that are behaviourally defined, with onset prior to age 3 years. Characteristic symptoms have been described as impairments in social communication, social interaction and imagination along with restricted interests and repetitive behaviours. Although these features are characteristic of all people with ASD, there is a range of severity and intellectual function. ASD tends to be more common in boys than girls. There is no evidence of any association of ASD with social class or ethnicity.

There are two approaches to the conceptualisation of ASD: the "categorical" and "dimensional" approaches.

2.1 Categorical approach

The categorical approach is used in the DSM-IV-TR[1] and ICD-10[2] classifications *(refer Annex A on page 85)*. In this approach the different disorders associated with autism (such as Asperger syndrome and atypical autism) are seen as distinct disorders, although the observed behavioural symptoms may overlap. The assumption is that they represent qualitatively different conditions. Research has supported the reliability and validity of the 3 diagnostic criteria that are central to the definitions used in DSM-IV and ICD-10; namely, social abnormalities; impairments in communication; and restricted repetitive and stereotyped patterns of behaviour.[3-5] It is to be noted that using either DSM-IV or ICD-10 increases the reliability of the diagnostic process, and the effect is even greater when inexperienced practitioners are making the diagnosis. No studies have so far compared which of the 2 systems (DSM-IV or ICD-10 systems) is the superior classification system.

Notwithstanding the increased reliability of diagnosis, some practitioners have raised concerns regarding the DSM-IV-TR and ICD-10 classification. For example, the categorical approach to autism assumes that a clear qualitative distinction can be made between autism and other pervasive developmental disorders. In practical terms, strict adherence to diagnostic criteria may result in some children (such as those who may meet the criteria for Pervasive

Developmental Disorders – Not Otherwise Specified, PDD-NOS) being excluded from receiving appropriate intervention services.

2.2 Dimensional approach

Arising from the dissatisfaction with the categorical approach, a dimensional approach to the diagnostic classification of autism has been proposed[6, 7] whereby the 'triad of impairments' is used as a defining parameter, including:

1. difficulties with social communication
2. difficulties with social interaction
3. difficulties with social imagination

Using the dimensional approach, children with a wide variety of clinical conditions would thus be seen as having 'autism spectrum disorders' or ASD. The dimensional concept of Autism Spectrum Disorders, or ASD, includes all the pervasive developmental disorders as defined in DSM-IV-TR and ICD-10. The spectrum is in fact wider, as it includes even subtle manifestations of the triad. However, no reports have thus far validated the breadth and scope of features that are subsumed as a part of a single autistic continuum, implicitly implied by the concept of the triad of impairments.

There are strengths and limitations when using either the categorical or dimensional approach for a diagnostic classification of ASD. However, given the balance of evidence, it is recommended that:

C All professionals involved in diagnosing ASD in children should consider using either the ICD-10 or DSM-IV-TR systems of classification.

Grade C, Level 2+

For the purposes of this CPG, the umbrella term ASD will be used in its broadest sense to include the sub-groups found in the category of 'Pervasive Developmental Disorders' (PDD), as defined in the ICD-10 (research criteria) and DSM-IV-TR. It includes Autism (299.00), Asperger syndrome (299.80) and children with similar features who are categorized as PDD-NOS (299.80) in the DSM-IV-TR, as well as Childhood Autism (F84.0) and Atypical Autism (F84.1) in the ICD-10. Childhood Disintegrative Disorder and Rett's Disorder (under the PDD umbrella in DSM-IV-TR) will be excluded in this CPG.

3 Surveillance

Developmental surveillance is the on-going process of identifying the child at risk of developmental delay, deviance or abnormality. Surveillance for features of ASD should be part of a general developmental surveillance programme involving parents or caregivers, early childhood educators as well as healthcare professionals (nurses, primary care doctors and paediatricians).[8]

D Professionals should aim to identify ASD early. Early identification provides opportunity for early referral and intervention, so that the child with ASD may have improved functioning in later life.

Grade D, Level 3

Early identification may be achieved by:

a. developmental surveillance of all children so that deviations from normal may be detected early
b. valuing and addressing parental and/or caregiver concerns about development
c. prompt access to diagnostic services

GPP Parents' or caregivers' attention should be drawn to the parental checklist(s) in the Health Booklet (provided to parents at the child's birth) that describes normal development in children. Parents should be encouraged to inform their healthcare professional if they suspect delay or abnormality in their child's development or behaviour.

GPP

Parental or caregiver concerns about communication, development and behaviour are highly sensitive and specific. In fact, parents or caregivers may notice concerns in the child's development as early as 18 months of age. In contrast, the absence of parental concern does not mean that the child's developmental skills are normal.[9]

C Parental or caregiver concerns about communication, interaction and play skills as well as behaviour should be elicited in a general developmental surveillance programme. Healthcare professionals should be aware that parental or caregiver concerns regarding delayed or deviant development are as important as clinically abnormal or atypical features.

Grade C, Level 2+

There are a number of barriers to early diagnosis. These include the failure to recognise warning signs, denial of problems, failure to be referred, long waiting times for initial appointment(s), inadequately trained staff in diagnosis and separate waiting lists for each professional group. In particular, early identification depends upon a primary healthcare professional being alerted to the "key signs" of ASD (*refer to Annex B on page 90*) during developmental surveillance and initiating a referral for further diagnostic assessment in a timely manner.

Local surveys suggested that the level of awareness and knowledge in childhood developmental and behavioural disorders among general practitioners and early childhood educators could generally be improved to facilitate timely referral for early assessment and intervention.[10, 11] Education and training programmes in developmental pediatrics should be developed to equip healthcare professionals and early childhood educators to identify children suspected with ASD and refer for assessment.

D All professionals who deal with pre-school children, whether in health care services or early childhood education centres, should receive training on the "key signs" that suggest a diagnosis of ASD.

Grade D, Level 4

In Singapore, primary healthcare professionals perform developmental surveillance and immunization for children at 4-6 weeks, 3-4 months, 6-10 months, 15-18 months, 2-3 years and 4-6 years. Whilst a high level of vigilance for features of ASD should be part of the surveillance on any of these occasions, a more pro-active stance during two key developmental stages, namely, at 18 months and 24-36 months would assist in early identification of children at risk of ASD. Even when developmental surveillance at 18 months appears to be normal, vigilant tracking of development 6 to 18 months later i.e. at 24 to 36 months is still recommended. This is because typical ASD behaviours may not always be evident in children under 24 months of age.[12-14] Furthermore, absence of prototypical behaviours of ASD does not and should not rule out possibility of diagnosis.

D Active surveillance by healthcare professionals is recommended at 18 months and again at 24-36 months for key signs of ASD.

Grade D, Level 3

Surveillance is important at an early age because studies showed that a valid clinical diagnosis of ASD could often be made by the time the child is 2 to 3 years old by experienced healthcare professionals.[15, 16] Other studies demonstrated that problems with eye contact, orienting to one's name, joint attention, pretend play, imitation, non-verbal communication, and language development were measurable by 18 months of age.[16] These symptoms were stable in children from toddler age through pre-school age. Furthermore, it had been shown that retrospective analysis of home videotapes identified behaviours that distinguished infants with autism from other developmental disabilities as early as 8 months of age.[17-19]

Diagnosis will generally be more difficult in young children who have high cognitive functioning, as well as in those with severe general developmental delay (for example, children with a mental age below one year old). Notwithstanding the difficulty, children of any age with specific clinical features suggestive of ASD should be referred for comprehensive evaluation.[13, 20, 21]

D Children with one or more of the following clinical features must be referred promptly for comprehensive developmental evaluation:

a. No babble, pointing or other gesture by 12 months,
b. No single words by 18 months,
c. No spontaneous (non-echoed) 2-word phrases by 24 months,
d. Any loss of language or social skills at any age.

Grade D, Level 4

4 Screening

Screening consists of using a standardised tool to detect ASD at a specific age in a general population of children. An ideal screening test is one with relatively few false negatives (i.e. test result is negative despite presence of disease), resulting in high sensitivity, such that positive cases will not be missed at screening. There are two levels of screening, namely, primary screening and secondary screening. Primary screening is conducted on a general population who has not been identified as being at-risk before testing, while secondary screening is conducted on a select group within the population who has been identified as being at-risk.[22-24]

No single ASD-specific screening instrument has been identified as ideal for primary screening of a general population of children. Current evidence suggests that the CHecklist for Autism in Toddlers (CHAT) at 18 months and Modified CHecklist for Autism in Toddlers (M-CHAT) at 18–24 months are useful for primary screening of ASD.[25-27] However, validation of CHecklist for Autism in Toddlers (CHAT) and Modified CHecklist for Autism in Toddlers (M-CHAT) will be necessary before they can be considered for use as a primary screening tool for the local population.

C In the general population, screening for ASD is not recommended.

Grade C, Level 2++

Secondary screening for ASD is highly recommended in high-risk populations. These include those with developmental, emotional and behavioural problems, specific syndromes or with family members diagnosed with ASD.[28-30] Secondary screening is recommended using standardised ASD-specific tools that have good validity and reliability in the local population. The use of Modified CHecklist for Autism in Toddlers (M-CHAT) or CHecklist for Autism in Toddlers (CHAT) may refine the risk of ASD but must not be used to rule out ASD.[25-27]

Other tests that may be considered include Pervasive Developmental Disorders Screening Test-II (PDDST-II), Screening Tool for Autism in Toddlers and Young Children (STAT), Social Communication Questionnaire (SCQ), formerly known as Autism Screening Questionnaire (ASQ) and Childhood Autism Spectrum Test (CAST).[31-34] Although these tests have not been validated in the local population, they remain useful for surveillance and secondary screening.

C In a high-risk population, screening for ASD is highly recommended.

Grade C, Level 2+

5 Assessment

Diagnosis of ASD is a complex process. Where possible, multi-disciplinary or trans-disciplinary assessment should be conducted to identify different aspects of ASD and help make accurate diagnoses.[35-38] Ideally, the team should consist of a variety of professionals who are experienced with developmental disorders and specifically with the variety of presentation of ASD. The team could include practitioners such as a developmental pediatrician, child psychiatrist, developmental or child psychologist, speech and language pathologists, occupational therapist and a specialist educator. A multi-disciplinary assessment is typically done sequentially, i.e. with each professional conducting an evaluation focusing on their respective areas of expertise. The results are then integrated and a diagnosis formulated. In contrast a trans-disciplinary assessment is usually conducted jointly, for example: an "arena assessment" in which any professional may evaluate a specific developmental area such as play skills, with the other professionals observing and inferring functioning. However personnel with this level of expertise in Singapore are few and organizing such sessions is resource intensive. Therefore when such a large team is not available, assessment to diagnose ASD may be conducted by smaller teams (such as two-member teams) or an individual practitioner with recognized training and who is very experienced with ASD.

A child suspected to have ASD following an initial screening should be referred for specialist assessment. A specialist assessment should include ASD-specific history-taking, clinical observation and obtaining wider contextual and functional information of the child's social and communication behaviour. In addition, the pre-school child with ASD should undergo clinical and neurological examination by a medical practitioner to determine possible etiologies, exclude treatable conditions and identify co-morbid medical conditions.

The purpose of the specialist assessment is to

a) review functioning in relevant domains;
b) confirm the diagnosis based on presenting symptoms;
c) provide an individualised profile to facilitate intervention

D Diagnostic evaluation of a child suspected to have ASD should be carried out by a multi-disciplinary team or professional who is trained and experienced with diagnosis of ASD. Evaluation includes:

a) an ASD-specific developmental history,
b) direct observations,
c) obtaining wider contextual and functional information.

In addition, the pre-school child with ASD should undergo thorough clinical and neurological examination to exclude associated medical conditions.

Grade D, Level 4

5.1 ASD-specific developmental history

An ASD-specific developmental history is important to understand reported behaviours in context. A framework designed to systematically elicit information about the child's current problems and developmental history is useful. Taking the history of the child's social and communicative behaviour does not substitute for direct observation and should be done in conjunction with direct observation of the behaviour. An ASD-specific developmental history should be taken using an appropriate framework.

Some examples of an appropriate framework include the Autism Diagnostic Interview – Revised and the Diagnostic Interview for Social and Communication Disorders. The Autism Diagnostic Interview – Revised (ADI-R), based on the categorical system, is a reliable diagnostic instrument.[39, 40] However, it should be used with caution in children with a developmental age that is below two years old.[41] The Diagnostic Interview for Social and Communication Disorders (DISCO), based on the dimensional system, has adequate inter-rater reliability for ICD-10 categories.[42, 43] Whilst administration of either ADI-R or DISCO is time-consuming, they should be utilised when necessary to aid in the diagnostic process. Practitioners utilising these instruments should be trained in their use and be aware of both local developmental and cultural practices.

C ASD-specific instruments should be considered when taking a developmental history as it increases the reliability of an ASD diagnosis.

Grade C, Level 2+

5.2 Direct observation

Clinical observation and assessment of the child's social and communication behaviours needs to be obtained through direct interaction with the child. Professionals need to have substantial training and experience to carry out such observation and evaluation of relevant behaviours. It may sometimes be impossible to obtain sufficient information within one session. In such situations, focused observations should be taken across more than one setting and information about the child's functioning in other relevant settings (especially in unstructured activities and social play with peers) should be routinely obtained.[44] Where direct observation is not feasible, interviews with relevant persons should be conducted.

D Professionals should conduct direct observations of the child's social and communication skills as well as behaviours.

Grade D, Level 4

GPP Information about a child's functioning in relevant community and educational settings should be routinely obtained either through direct observations or interviews with relevant persons.

GPP

ASD-specific observational instruments are available to aid in the process of observation. The Autism Diagnostic Observation Schedule - Generic (ADOS-G) is a reliable diagnostic instrument that can be used to enhance clinical history-taking.[45] It uses a series of structured social contexts designed to elicit, observe and evaluate relevant social and communicative functioning. Current evidence shows that the ADOS-G has excellent diagnostic validity for differentiating autism from non-ASD conditions, when controlled for expressive language.[45] The Childhood Autism Rating Scale (CARS) is another standardised instrument used to observe spontaneous behaviours associated with autism. However, there is limited research on its use in children who are under 3 years old.[46]

C ASD-specific observational instruments should be used to increase the reliability of diagnosis.

Grade C, Level 2+

6 Prognosis

A common concern of parents is the long-term prognosis for the child diagnosed with ASD. Prognosis in a child with ASD depends on a variety of outcomes such as communication skills, cognitive skills, self-care skills and independent living skills.

Amongst studies that examined the course and prognosis of children diagnosed with ASD before the age of 3 years, early regression of language skills was not associated with poor prognosis because most children regained the lost skills.[47,48] Other studies suggested that a lack of early joint attention and imitation[49,50], as well as failure to develop functional speech by 5 years of age were predictive of poor outcome.[51, 52]

Cohort studies showed that high intelligence quotients (IQ) and language skills in children with ASD were independently associated with better outcomes.[53-56] The studies noted that social impairment and repetitive behaviours could still be present when these children grew up.

It is difficult to reliably predict later prognosis in children who are diagnosed with ASD before they are three years old.

GPP In children diagnosed with ASD before three years old, parents should be advised that it is difficult to reliably predict prognosis, because individual outcomes are extremely variable and depend on many factors.

GPP

7 Aetiology

The aetiology of ASD is multi-factorial. Genetic influences as well as prenatal, perinatal and postnatal environmental factors had been proposed as possible causes for ASD. However, the role that each of these factors plays in the aetiology of ASD is less well understood and continues to be the subject of research.

7.1 Genetic influences

There is a strong role for genetics in the aetiology of ASD, based on epidemiological evidence.[57-59] Twin studies and family studies indicate that the heritability estimates of ASD are >90%.[60, 61] Many genetic defects are associated with ASD. Some defects occur singly (e.g fragile X syndrome) while others are minor mutations that interact with other genes additively or synergistically to produce the ASD phenotype. Results of population studies are consistent with a multi-factorial inheritance, although the exact genetic model for ASD is currently controversial. Environmental factors have been implicated in the causation of ASD as a sole agent or possibly via a "second-hit" phenomenon during foetal brain development to modulate manifestation of ASD in individual children.[57, 60, 62-64] ASD is classified into secondary (or syndromic) and idiopathic causes.

7.1.1 Secondary ASD

Secondary ASD refers to cases associated with a medical condition or genetic abnormality. Generally reported success rates for identifying a major single etiology in individuals with ASD is 6-15%,[65-69] but may be as high as 40%.[69-71] It is crucial to distinguish secondary from idiopathic ASD, because many are inheritable and recurrence risks are different. Conditions associated with ASD include (but are not limited) to:

- Fragile X syndrome
- Other chromosomal abnormalities
- Tuberous sclerosis (TS)
- Mitochondrial disorders
- Soto syndrome

- Gene mutations including the MEthyl-CPG-binding Protein 2 (MECP2)[72] and Phosphatase and TENsin homolog (PTEN) gene mutations[73]

Fragile X syndrome is a genetic syndrome that is most commonly associated with ASD.[72-74] The classical phenotype of the Fragile X syndrome consists of mental retardation, macrocephaly, large pinnae, large testicles (particularly after puberty), hypotonia and joint hyper-extensibility. Fragile X syndrome is caused by expansion of the CGG trinucleotide repeat in the *FMR1* gene into a full mutation (>200 CGG repeats). The *FMR1* gene is located on the X chromosome.[75, 76] A very small percentage of children with autism have Fragile X syndrome. On the other hand, about 30-50% of individuals with Fragile X syndrome demonstrate some characteristics of ASD. Families with the Fragile X mutation may show highly variable patterns even in affected family members. The variable physical phenotype makes clinical diagnosis difficult. For this reason, molecular genetic testing for Fragile X syndrome should be offered for children who present with ASD.[77-80] The diagnostic yield of Fragile X syndrome testing in the evaluation of ASD is about 5% (range 0%-8%) depending on prevalence of associated intellectual disability.[69-71] DNA analysis for Fragile X syndrome is preferred over cytogenetic analysis, because cytogenetic testing has low sensitivity, especially in affected females. In families with Fragile X syndrome, DNA analysis can be used to determine the status of family members and risk of having affected children. Risk prediction may be complex, so formal genetic counselling is recommended.[80]

Approximately 3% of individuals with autism have a maternally inherited chromosomal duplication in the Prader-Willi/Angelman syndrome region of 15q11-q13. An additional 3-5% of individuals with autism have other chromosome abnormalities, including apparently balanced and unbalanced translocations, inversions, rings, interstitial deletions and duplications, and marker chromosomes.[79, 81] Although chromosomal abnormalities associated with ASD are found on almost every chromosome, only a few occur commonly enough to be regarded as possible indicators of putative autism genes. Chromosome abnormalities (in addition to 15q duplications) that have been reported more than once are deletions of chromosomes 2q, 2p37, 16p11.2, 17p11, 18q, 22q11, 22q13, Xp, as well as the sex chromosome aneuploidies, 47,XYY and 45,X.[82, 83]

17% to 60% of intellectually disabled individuals with tuberous sclerosis (TS) have associated ASD and epilepsy.[84-87] The number of ASD individuals with TS was estimated to be 0.4-3%, increasing to 8-14% if epilepsy was also present.[84, 86, 88, 89]

In children with ASD presenting with atypical features such as hypotonia, failure to thrive and recurrent episodes of regression or flare-ups, mitochondrial disorders may be considered in the diagnosis.

Soto syndrome may be considered in the differential diagnosis of children with autism who have macrocephaly and overgrowth.

7.1.2 Idiopathic ASD

Idiopathic ASD is diagnosed when no underlying cause is identified after thorough physical examination and appropriate testing. The recurrence risk to siblings of individuals with idiopathic autism is 4% for autism (range 2-8%) and an additional 4-6% risk for milder symptoms, including language, social, and psychiatric disorders.[57, 62, 90, 91] In families with two or more affected children, recurrence risks ranged from 25 to 35%.[92]

C Parents of children with ASD may require genetic counselling regarding the risk of recurrence of ASD in the next pregnancy.

Grade C, Level 2+

7.2 Role of prenatal, perinatal and postnatal risk factors

Studies showed that children diagnosed with ASD had increased umbilical cord blood levels of specific neuro-trophins and neuro-peptides.[93] Matched case-control studies suggested that children with ASD were more likely to have been first-born children[94] with increased risk of antenatal complications[94] and neonatal encephalopathy[95] as compared to their non-ASD siblings. In a large meta-analysis of 40 studies examining over 50 prenatal factors, factors associated with autism were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first-born *vs.* third or later, and having a mother born abroad. Factors in which there was strong evidence against the risk of autism included previous fetal loss and maternal hypertension, proteinuria, pre-eclampsia and swelling.[96] In another case-control matched study, the

prenatal factors that occurred significantly more often among children with ASD than those without were advanced maternal age and parity. There was a small but statistically significant increased duration of education among mothers of children with ASD than those without. Significant perinatal factors associated with ASD were breech presentation and primary caesarean delivery. When corrected for breech presentation which is a known indication for caesarean delivery, the association between primary caesarean delivery and ASD was eliminated. No significant associations were found between ASD and neonatal factors.[97]

7.3 Lack of role of the MMR (measles, mumps, rubella) vaccine

Multiple epidemiologic[98-104] as well as population-based studies conducted in Finland, Denmark, United States, Japan, Sweden and Great Britain had confirmed that no association existed between MMR vaccines and the development of autism or gastrointestinal symptoms in children with ASD.[105-108]

The link between the MMR vaccine and gastro-intestinal lymphoid hyperplasia was first suggested in 1998 in 12 children who had autistic regression and chronic diarrhoea. This association was criticised on grounds that the symptoms were based on parental memory of onset of behavioural problems after the MMR vaccine and likely related to recall bias.[109] This was followed by the isolation of measles RNA fragments from intestinal material.[110] Subsequently, many of the original authors questioned the proposed relationship between gastro-intestinal lymphoid hyperplasia and autism, since the reported ileal inflammation was non-specific.[111,112] The British Medical Research Council,[113] World Health Organization[114] and American Medical Association[115] announced that there was no evidence to link MMR vaccines with inflammatory bowel disease or autism.

It is a well-known fact that children who are not immunized and subsequently become infected with the measles virus may develop encephalitis leading to autistic regression. The risk of autistic regression following measles encephalitis is about 1 in 1,000 to 10,000 cases. Vaccination against measles, mumps and rubella

infections therefore remains vital in prevention of these highly contagious childhood infections.

B Parents should be educated to proceed with their child's vaccination schedule, including the MMR vaccine.

Grade B, Level 2+

7.4 Lack of role of thimerosal - containing vaccines

Many studies found no consistent association between thimerosal-containing vaccines and autism.[116-120] Thimerosal preservative in vaccines has been proposed as a reason for an increased prevalence of autism, because thimerosal contains 50% ethylmercury and mercury is known to be neuro-toxic. This was based on 3 epidemiologic studies that showed an association between thimerosal exposure and neuro-developmental delay, including autism.[121-123] These studies were later criticised because they contained serious methodological flaws and used non-transparent analytical methods.[124] Several retrospective and well-designed prospective cohort studies confirmed that the incidence of autism increased throughout the study period and continues to increase,[116, 117] even though thimerosal had been removed as a preservative in vaccines since 2001.[125] The 2004 Immunization Safety Review Committee of the Institute of Medicine[124] as well as a well-conducted systematic review[126] separately concluded that there is insufficient evidence for a causal relationship between exposure to thimerosal and neuro-developmental disorders.

B Parents should be reassured that ASD is not associated with thimerosal-containing vaccines.

Grade B, Level 2+

7.5 Lack of role of inflammation and infection

No neuro-imaging studies demonstrated inflammatory changes to the brain, meninges or vasculature of the brain to support an obvious inflammatory process within the central nervous system as a cause of autism.[127] Similarly, there is no conclusive evidence of a specific infectious agent that could trigger the development of autism.[128, 129]

8 Investigations

The aims of investigating children with ASD are to:

a) diagnose associated syndromes, such as Fragile X syndrome, tuberous sclerosis, fetal alcohol syndrome and Prader-Willi/Angelman syndrome; (*Refer to Chapter 7).*

b) diagnose an underlying disorder that requires treatment such as an inborn error of metabolism;

c) confirm the presence of a co-morbidity that requires early treatment such as seizures.

In most children with ASD, the cause is idiopathic. Only a minority of children with ASD (about 6-15%) has an associated medical condition. The proportion with an associated medical condition varies, depending on how extensively the child is investigated and the severity of learning disability.[130-134] The majority of children with ASD do not require extensive investigation. Excessive investigation subjects the child to procedures that may cause unnecessary pain and/or discomfort, and results in increased costs to the parent/caregiver.

D The pre-school child with ASD may require specific medical investigations based on history and clinical examination.

Grade D, Level 4

8.1 Hearing evaluation

Diagnosis of ASD in a child does not exclude diagnosis of hearing loss. Studies showed that conductive, sensori-neural or mixed hearing loss can co-occur with ASD and that some children with ASD may be incorrectly thought to have peripheral hearing loss.[135-138] Hearing loss in children may develop later on in childhood, even if the hearing screen was documented to have been normal at birth.

C Children with ASD should have a complete audiologic assessment to obtain comprehensive information on their hearing status including middle ear function.

Grade C, Level 2+

Hearing thresholds may be established using age-appropriate behavioural tests such as visual reinforcement audiometry, play audiometry or pure tone audiometry. If reliable hearing thresholds cannot be obtained, electro-physiological tests such as oto-acoustic emissions (OAE), auditory brain-stem response (ABR) or auditory steady-state response (ASSR) are the gold standards and at least provide an accurate estimate of hearing and auditory nerve function. Since electro-physiological tests are time-consuming, the child with ASD may require sedation or even general anesthesiae for the test to be completed. Click-evoked ABR measurements are attempted first as they are a quick method to obtain hearing thresholds at 2–4 KHz, especially for sensori-neural hearing loss. If the child is suspected with hearing loss (ABR threshold > 20dB nHL), frequency-specific ABR will confirm the diagnosis.[139-142]

C Where the hearing status of a child cannot be determined by age-appropriate behavioural audiometry, electro-physiological tests such as OAE, ABR or ASSR is recommended to at least provide good estimates of hearing thresholds.

Grade C, Level 2+

8.2 Genetic evaluation

Given the strong role of genetics in the aetiology of ASD, children with features suggestive of chromosomal abnormality should be investigated. *(Refer to Chapter 7)*.

D Children with ASD with the following features should have a genetic evaluation:

a) microcephaly or macrocephaly
b) a positive family history (of a genetic syndrome)
c) dysmorphic features

Grade D, Level 3

Studies reported that about 5% of children with ASD have Fragile X syndrome,[69-71] while 30-50% of individuals with Fragile X syndrome have characteristics of ASD.[77-80] Diagnosis of Fragile X syndrome is important for genetic counselling purposes, since it has implications for family members.[13, 143-146]

In Singapore, it is estimated that genetic evaluation of children diagnosed with ASD may detect 5% with Fragile X syndrome (through DNA analysis) and 5% with chromosomal abnormalities (through high-resolution chromosomal analysis).[69,70] Tests for the MECP2 and PTEN gene mutations are not available in Singapore at the time of writing this guideline.

D Children with ASD may be offered high-resolution chromosomal studies and DNA analysis to look for an associated medical condition following diagnosis.

Grade D, Level 3

8.3 Metabolic testing

Less than 1% of children with ASD have an inborn error of metabolism.[132] Clinical findings suggestive of an inborn metabolic error include lethargy, cyclic vomiting, encephalopathy, seizures, dysmorphic features and intellectual impairment. Diagnosis of an inborn metabolic error may be important for treatment and genetic counselling purposes, since most have Mendelian inheritance.[147-149]

C Children with ASD may be offered selective metabolic testing when an inborn error of metabolism is suspected.

Grade C, Level 2+

8.4 Brain imaging

Although brain abnormalities have been reported in ASD, these were inconsistent and no pattern of localization was found. Brain imaging may be considered in children with ASD who have clinical neurological abnormalities.[150-153]

C Brain imaging is not routinely recommended in children with ASD.

Grade C, Level 2+

8.5 Electro-encephalography (EEG)

The prevalence of epilepsy in children with ASD has been estimated at 7-14%. Seizure onset has 2 peaks: at less than 5 years old and again in adolescence. Mental retardation, with or without motor

abnormalities and family history of epilepsy, was a significant risk factor for the development of seizures in individuals with ASD.[154-158]

C Electro-encephalography (EEG) is not routinely recommended in children with ASD but should be considered if any of the following are present:

a) clinical seizures
b) symptoms suggestive of sub-clinical seizures such as staring spells
c) a history of developmental regression.

Grade C, Level 2+

8.6 Lead screening

Serum lead levels in children with ASD are typically not in the toxic range. However, children with developmental delays may spend an extended period of time in the oral–motor developmental stage. It has been suggested that developmentally delayed children be screened for lead, a treatable neuro-toxin particularly if pica is suspected.[159]

D Serum lead screening is not routinely indicated in children with ASD but may be considered where there is clinical suspicion of pica.

Grade D, Level 4

8.7 Food allergy screening

Several studies confirmed that most children with ASD do not have associated atopy, asthma, food allergy and primary immunodeficiency. The innate immunity of children with ASD is not different from that of normally developing children.[160, 161]

C Food allergy tests are not recommended in the routine assessment of children with ASD.

Grade C, Level 2+

8.8 Hair mineral analysis

In a case controlled study, no difference in concentration of calcium, magnesium, zinc, copper, lead and cadmium in scalp hair samples was found between children with and without ASD. No evidence of

toxicity or deficiency of minerals was found and hair mineral analysis had no impact on management.[162-166]

C Hair mineral analysis is not recommended in the evaluation of children with ASD.

Grade C, Level 2+

8.9 Immunologic evaluation

A study showed that children with ASD have normal immune function.[167] Immunologic evaluation of children with ASD may be indicated in the presence of recurrent infections.

C Immunologic investigation is not routinely indicated in children with ASD.

Grade C, Level 2+

8.10 Assay of vitamin B6 and magnesium

A Cochrane systematic review on the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication, and behavioural responses of children and adults with ASD concluded that no recommendation could be made regarding the use of B6-Mg as treatment for autism due to the small number of studies.[168]

C Assay of vitamin B6 and magnesium levels is not recommended in children with ASD.

Grade C, Level 2+

8.11 Assay for yeast overgrowth in stools

Yeast is a normal commensal in the bowel and stool of normal children. Candidial overgrowth has not been documented by endoscopy in the bowel of children with ASD.[109]

C Investigations to identify yeast over-growth in the gastro-intestinal tract are not recommended in children with ASD.

Grade C, Level 2+

9 Management: Intervention

The objectives of intervention are to promote child health and well-being, enhance emerging competencies, minimize developmental delay, remediate disabilities, prevent functional deterioration, promote adaptive parenting and overall family functioning. These goals are accomplished by providing individualized developmental, educational and behavioral intervention services for children in conjunction with mutually planned support for their families.[169] Interventions may be regarded as either mainstream or alternative (*Refer to Chapter 12*).

The range of activities that constitute intervention should be viewed holistically, and includes the child's involvement in structured centre-based activities, as well as parent-mediated intervention and structured positive engagement with parents/caregivers at home. A wide range of interventions is increasingly available in Singapore. Some professionals offer a combination of interventions that utilize various elements of different methods when providing intervention for a particular child. The efficacy and safety of any intervention must be validated through well-designed research. At the time of publication of this guideline, available literature on interventional studies was often found to be neither of high quality nor rigorously planned.

Intervention is best planned and carried out by professionals together with the child's parents and caregivers. Skills can be developed and practiced in a range of settings, for example, centre-based programmes, home-based programmes or parent-mediated intervention. Parent-mediated intervention is a source of quality intervention for the pre-school child with ASD, and should be considered as part of the child's total intervention plan, along with attendance at structured centre-based intervention programmes.

Intervention may be provided by different professionals who are each able to teach the same behaviour or skill set. For example, psychologists, teachers and speech and language therapists in partnership with parents and caregivers often provide interventions for social communication skills because developing receptive and expressive skills are fundamental to the ability to perform in a class. Similarly, teachers, psychologists and occupational therapists in partnership with parents and caregivers may address challenging behaviours in the child with ASD. It is crucial to formulate an

individualized plan with input from a variety of specialists, in response to the shifting developmental needs of the child with ASD.

D Every pre-school child diagnosed with ASD should have an individualised intervention plan that sets out the goals, type(s), frequency and intensity of intervention, in order to address particular developmental and educational needs.

Grade D, Level 4

D An individualised intervention plan should consist of a variety of quality programmes and activities. This includes attendance in comprehensive early intervention programmes, programmes targeting specific needs and also positive engagement with parents and/or caregivers.

Grade D, Level 4

Timing and intensity of intervention

Most children with ASD show marked progress during the period they receive early intervention (two to six years) and nearly all children with ASD show some benefit.[51, 170-172] However, there are no studies to support claims of recovery from ASD as a consequence of early intervention. There is no evidence to suggest that any single type of intervention is effective for all children with ASD.[51, 170]

C All pre-school children with ASD should undergo early intervention as soon as significant developmental need is recognized by a trained professional because outcomes improve with early intervention.

Grade C, Level 2++

The intensity of early intervention required in order to effect positive change is highly variable.[51, 170] While some studies reported a need for an intervention duration of 40 hours a week[173], others suggested that an hour a week of parent training could result in positive outcomes.[174] The National Academy of Sciences suggested that intervention should be on-going and "include a minimum of 25 hours a week, 12 months a year, in which the child is engaged in systemically planned, and developmentally appropriate educational activity toward identified objectives. What constitutes these hours, however, will vary, according to a child's chronological age, developmental level, specific strengths and weaknesses, and family needs."[51]

D The intensity of intervention should be continually monitored and varied according to the child's changing needs.

Grade D, Level 4

Intervention programmes for the pre-school child with ASD may be divided into:

- Comprehensive Early Intervention Programmes
- Interventions addressing specific needs
- Intervention models or approaches

9.1 Comprehensive early intervention programmes

It is difficult to define a comprehensive early intervention programme for the child with ASD. No outcome studies have so far been published in a peer-reviewed journal to support the superiority of one programme over another.[51, 170, 171]

Selection of a comprehensive early intervention programme is based on the following:

a) engagement of the child in a systematically planned, and developmentally appropriate intervention activity with clear objectives
b) provision of sufficient individualised attention on a daily basis;
c) intervention that is targeted for the specific needs of the child and delivered in a variety of settings, including functional spontaneous communication, social instruction, cognitive development and play skills;
d) utilisation of pro-active approaches for the management of challenging behaviour;
e) inclusion of occasional activities that would enable planned interactions to occur with typically developing children.

In Singapore, services that contain elements of comprehensive early intervention programmes are typically provided by, but not restricted to, the Early Intervention Programme for Infants and Children (EIPIC)[iii] administered by the National Council of Social Service

[iii] Information on EIPIC can be accessed at www.cel.sg

(NCSS) under the purview of the Ministry of Community Development, Youth and Sports (MCYS).

9.2 Interventions addressing specific needs

These include:

9.2.1 Interventions for communication impairments
9.2.2 Interventions for social skill impairments
9.2.3 Interventions for challenging behaviours
9.2.4 Interventions for associated difficulties

9.2.1 Interventions for communication impairments

The process of developing communication skills is a complex one requiring the acquisition of fundamental skills, such as joint attention, auditory processing, understanding of symbols (e.g. interpretation of gestures, use of everyday objects) and social cues (e.g. facial expression, intonation, volume of voice). Such skills are crucial for the typically developing child to develop comprehension and expressive skills. These skills, in turn, are vital when language is utilized for building and maintaining relationships, solving problems and learning new concepts.

Impairment in communication is a core issue in all children with ASD. Comprehensive assessment of communication ability by a speech and language therapist is essential prior to formulation of intervention plans.

D Interventions for impaired communication should address the development of pivotal skills such as spontaneity, initiation, motivation and self-regulation.[175]

Grade D, Level 4

A Interventions for impaired communication should aim to increase joint attention and symbolic play in order to improve expressive language development.[176]

Grade A, Level 1+

D There is no single language or communication intervention method that is appropriate for all children with ASD. The optimal communication intervention for an individual child with ASD depends on the needs of that particular child.[177]

Grade D, Level 4

Interventions for impaired communication may utilize verbalization, alternative-augmentative communication (AAC) systems and/or visual strategies. AAC systems allow communication skills to be maximized in children who have not yet developed speech or have poor verbal communication. AAC systems match the visual processing strengths and cognitive profile of children with ASD. Some methods of providing AAC involve supplementation or replacement of speech and/or writing with photographs, line drawings (as in Picture Exchange Communication System, PECS), tangible objects and symbols (such as manual signs, gestures and finger spelling).

AAC systems may be categorized as low-tech (not requiring batteries, electricity or electronics) or high-tech (requiring electronic devices to store/retrieve messages, which can be connected to voice output).[178] The choice between low or high-tech AAC systems depends on understanding the communicative needs, cognitive ability and learning style of the child. Studies over the past 30 years demonstrated that AAC intervention resulted in a modest increase in speech production.[179] Nevertheless, functional speech may not always be stimulated in non-verbal children, since 5 of 6 participants using AAC remained at zero speech production in the systematic review.[179]

A Alternative-augmentative communication (AAC) systems may be recommended for pre-school children with ASD because they expand (spoken or written) communication, may stimulate speech acquisition in non-verbal children and enhance expression in verbal children.

Grade A, Level 1+

Visual strategies (including the use of photographs, line drawings, written words used singly or as part of schedules) are often used because these strategies capitalize on the comparatively stronger visual and spatial skills of the pre-school child with ASD. They provide structure and increase predictability, giving the child more time to process verbal instructions. Children diagnosed with Asperger

syndrome who have weak visual-perceptual skills may prefer written schedules.

A Visual strategies are useful interventions for children with ASD because they offer visual support to communication, increase spontaneous imitation and socially communicative behaviour.[180, 181]

Grade A, Level 1+

D Parent/caregivers should be educated that the use of AAC systems or visual strategies neither inhibits speech nor replaces the development of expressive spoken language skills.[182]

Grade D, Level 4

9.2.2 Interventions for social skill impairments

Social interaction difficulties are a core impairment of ASD, appear early, continue to manifest as the child grows and may be evident across different settings.[183] They are often the result of a lack of social awareness and limitation in social skills.

Social skills may be directly and explicitly taught to the child with ASD through modeling and feedback or reinforcement.[184-187]

Modeling is practiced when an adult or peer demonstrates the skill in real life or through video.[188] Feedback or reinforcement requires that the child with ASD is taught a specific behaviour (such as regulating voice volume) and given positive feedback (or other forms of reinforcement) when the behaviour is elicited in the appropriate situation.

D Social skills are best taught explicitly through modeling and feedback.

Grade D, Level 3

The goal of a social skills or social development programme is to help individuals with ASD to function as independently and socially effectively as possible.[183] Depending on the functioning level of the child, social skills programmes could include the following:

a. Assessment and teaching of social interaction in natural settings

Social interaction is best assessed when the child is in a variety of natural settings. Following assessment, the child is recommended to practice the social skills within natural activities and settings.[175] For example, in very young children with ASD, teaching joint attention[189] with adults/caregivers is an important goal, whereas seeking help becomes more important by the time a child enters school.[51] It is important for the child with ASD not only to learn social skills in a natural setting but also to learn to generalise the learnt skills across various settings and contexts.

b. Provision of structure, visual cues and predictability

This includes providing a pictorial, written or typed schedule and including activities that are predictable yet enjoyable. Social expectations need to be stated explicitly at the beginning of each teaching session (for example, expectations for turn-taking).[51, 183, 190, 191]

c. Making abstract concepts more "concrete"

Abstract concepts (for example, kindness, loudness, friendship) must be explicitly operationalized and differentiated from other behaviours. For example "When I do this, this is (or is not) kindness".[191]

d. Activities or programmes that include typically developing peers

Depending on the child's functioning level and readiness, opportunities for purposeful and appropriate interaction with typically developing peers would benefit the child in learning social interaction skills.[175, 183, 190, 191]

e. Fostering esteem

Some children with ASD experience peer rejection which in turn, discourages attempts at seeking social interaction, and perpetuates the cycle of isolation. Fostering self-appreciation and self-acceptance is important as part of a social skill programme.[183, 191]

For more able children with ASD, activities or programmes may need to teach the child how to attend to the interest and needs of others, instead of self.[51] Over time, the child with ASD learns to seek out information about interests of other children and develops group camaraderie.[191]

D Social skills programmes depend on the functioning level of the preschool child with ASD and may include

- Assessment and teaching of social skills interaction in natural settings
- Provision of structure, visual cues and predictability
- Making abstract concepts more "concrete".
- Activities that enable purposeful and appropriate interaction with typically developing peers.
- Goals focusing on fostering self-appreciation and self esteem

Grade D, Level 4

9.2.3 Interventions for challenging behaviours

Challenging behaviours usually have an underlying function or motive, including: a means of communicating needs more effectively; seeking social attention or preferred activities; avoiding difficult tasks and aversive situations; or the generation of sensory reinforcement in the form of auditory, visual, tactile, olfactory, and gustatory stimulation.[192,193] Examples of challenging behaviours include tantrums (crying), shouting, aggression, stereotypic behaviour and self-injury.[194] Functional analysis of the challenging behaviour should be conducted to develop alternative appropriate behaviours. These alternative behaviours serve the same function as the challenging behaviour.[194] Where a challenging behaviour is related to a lack of skills, intervention targeted at developing those deficit skills should be provided.

B Interventions for children with ASD with challenging behaviours based on functional behavioural assessment are recommended.

Grade B, Level 1+

While behavioural intervention using applied behaviour analysis methods was shown to be effective in reducing or eliminating specific challenging behaviours and teaching new skills to children and adults with autism or other developmental disorders,[172,195] no single

intervention has been shown to deal effectively with problem behaviours for all children with ASD. Positive behavioural interventions and support strategies may not be very effective for up to one-third of challenging behaviours which are related to sensory stimulation/issues. In these cases, different or additional strategies may be required.

9.2.4 Interventions for associated difficulties

Some children with ASD may experience associated difficulties such as:

- Perceptual and motor difficulties
- Nutrition and feeding difficulties
- Unusual sensory responses

9.2.4.1 *Interventions for perceptual and motor difficulties*

As children grow they master various developmental tasks in the gross and fine motor, perceptual and adaptive domains. Children occupy their time playing and learning as well as eating, getting dressed and grooming. In the process of learning these new skills they also learn to attend and self regulate. Children with ASD are often impaired in these tasks.

B Children with ASD who present with perceptual distortions, fine and gross motor co-ordination difficulties, impaired play skills and impaired self-care and adaptability may benefit from consultation with appropriate specialists such as occupational therapists and/or physiotherapists.

Grade B, Level 2++

9.2.4.2 *Interventions for nutrition and feeding difficulties*

Children with ASD may present with feeding difficulties, often eating a narrow range of foods that may be nutritionally inappropriate. Such difficulties may be attributed to rigidity, sensory difficulties, and deficits in social, communciation and executive functions, rather than behavioural non-compliance or developmental delay.[196, 197]

Rigidity in perception, planning and sequencing difficulties may lead to insistence on the same food at each meal, specific preparation methods, insistence on using a specific utensil and/or following extensive rituals

at mealtimes.[198-200] Fear responses in children with ASD are difficult to decipher as they may be irrational or unrelated to choking or vomiting.

Assessment of feeding difficulties in children with ASD are best carried out through in-depth caregiver interview and observation across meals (e.g. snacks, lunch) and settings (e.g. home, school).[197]

GPP In the assessment and management of feeding difficulties in children with ASD, the healthcare professional needs to consider challenges in executive functioning, fears, sensory processing, social and language skills.

GPP

Presentation of gastrointestinal disorders in children with ASD may manifest as behavioural changes, making the diagnostic evaluation complex. Behavioural management may need to be initiated concurrently while medical investigations for gastrointestinal disorders are ongoing.[201]

D Management of gastro-intestinal disorders and feeding difficulties in children with ASD may require collaboration between healthcare professionals such as primary care doctors, paediatricians, gastro-enterologists, dietitians and therapists.

Grade D, Level 4

9.2.4.3 *Interventions for unusual sensory responses*

45% to 95% of individuals with ASD present with significant and unique sensory behaviours such as extreme aversion to or excessive seeking of sensory stimuli.[202] This results in increased stereotypic, rigid and repetitive behaviours[203] and impacts on the ability to participate in daily life activities.[204] Children with ASD having unusual sensory responses may benefit from assessment and intervention based on occupational therapy, sensory integration and/or sensory-based interventions.[205]

Occupational therapists may modify the social and physical environment to manage sensory characteristics. Such support may reduce problem behaviours in children with ASD.[205]

D Environment, tasks and timing of activities of children with ASD should be adapted to minimize negative sensory reactions and meet their sensory needs.

Grade D, Level 4

Sensory integration intervention[206] uses child-directed and therapist-guided activities to challenge the child to actively participate in sensory activities and produce adaptive interaction and response.[206] While sensory integration intervention may enhance the ability to modulate behaviour and improve social interaction responses, the evidence for its efficacy is inconclusive.[204, 205]

Sensory-based intervention or sensory-stimulation intervention involves providing directly to the child, some form of sensory input (usually one type of sensation at a time) in expectation of a better modulated behavioural response. The child is usually a passive recipient of the sensory-stimulation e.g. touch, music, brushing (*Refer to chapter 12).*

D "Sensory integration" intervention is not recommended as standard therapy in management of children with ASD but may be considered where the child has sensory difficulties that affect daily functioning.

Grade D, Level 3

9.3 Specific intervention models

Several intervention models were developed based on specific psycho-developmental approaches. While some approaches are more estasblished than others, there are no studies to support the superiority of one intervention model over another.[51, 170] It is important to note that the features of and approaches used in many of the specific intervention packages discussed in this CPG can also be found in a variety of intervention progammes. The needs of the child, family preferences and availability of resources should be discussed when any specific intervention model or combination of approaches are considered.

9.3.1 Early Intensive Behaviour Intervention (EIBI)

Early Intensive Behaviour Intervention (EIBI) represents a specific approach within the broader class of 'applied behaviour analysis'

(ABA) interventions. ABA is often used synonymously with EIBI. The original home programme with interventionists typically lasted at least 2 years and involved about 40 hours of weekly intervention.[207] Recent systematic reviews showed that EIBI was efficacious but had variable outcomes, suggesting that EIBI was not effective for all children with ASD.[208, 209] No studies replicated the magnitude of efficacy reported by Lovaas (i.e., significant gains on intelligence tests and claims of 'recovery', as defined by a placement in mainstream schools without assistance).[173] Parents should be informed that EIBI, in its original form, is an expensive intervention that may place significant financial strain on families.

A Early Intensive Behavior Intervention (EIBI) can be recommended as an intervention option for children with ASD.

Grade A, Level 1++

9.3.2 Structured Teaching

Structured Teaching is the approach developed by the Treatment and Education of Autistic and related Communication-handicapped CHildren (TEACCH) at the University of North Carolina at Chapel Hill for the education of individuals with ASD.[183] Structured Teaching proposes that children with ASD learn better when provided with visual information to supplement auditory input and external organizational support. Evidence for Structured Teaching came from studies on child progress,[210, 211] parent teaching skills,[212] as well as the feedback of parents, trainees, and replication sites.[213] Recent studies in Hong Kong and Italy reported gains across a wide variety of adaptive domains.[214, 215]

C Structured Teaching can be recommended as an intervention option for children with ASD.

Grade C, Level 2+

9.3.3 Hanen "More Than Words®" programme

The Hanen "More Than Words®" programme was developed by the Hanen Centre in Canada for families of children with ASD and related social communication difficulties. It aims to teach parents to build communication and social interaction skills with their child through enhancing the parents' ability to observe, create structured routines with opportunities to initiate and respond and use naturally occurring

situations such as household tasks for joint attention. Research on the efficacy of the Hanen programme was limited. In one study, parents learnt interaction strategies that were likely to facilitate their child's development of communication.[216]

D The Hanen "More Than Words®" programme may be considered as an intervention option for children with ASD.

Grade D, level 3

9.3.4 Developmental models

Developmental- or relationship-based interventions focus on the child's ability to form positive, meaningful relationships with other people. Two developmental models available in Singapore are:

a. Developmental, Individual-difference, Relationship-based (DIR) or Floortime

The chief activities of the DIR/Floortime model occur during play ('floortime') sessions where interactive experiences are child-directed and occur in a low stimulus environment. The interactions aim to develop social relationships and socio-emotional growth.[217]

b. Relationship Development Intervention (RDI)

RDI focuses on increasing the motivation and interest in social relationships in children with autism. In RDI, the child is engaged in various activities with the aim of increasing social competence and enjoyment in social relationships.[218]

Studies examining the effectiveness of developmental interventions in children with ASD remained inconclusive.[171]

D Developmental models such as Developmental, Individual-difference, Relationship-based (DIR)/Floortime and Relationship Development Intervention (RDI) models may be considered as intervention options for children with ASD.

Grade D, Level 3

10 Family and caregiver support

Parents of children with ASD were reported to experience greater level of psycho-social and economic stressors relative to those with other disabilities.[219-222] Hence, management of the pre-school with ASD should include a family-centred perspective, focusing on the needs of the family, not only the child with ASD.

Sources of information and support for caregivers and the family

Parents and caregivers of children with ASD require on-going information to help them understand the diagnosis and make informed choices for intervention. In addition to general information about the nature of ASD, parents need information that is specific to the manifestations of ASD in their child, as well as up-to-date information about the intervention, educational and support options available.[223, 224]

Other than support from the immediate or extended families (e.g. grandparents, domestic help) parents and caregivers may seek support from external sources within the community. For example, "Parent support groups" are voluntary organizations whose goals are to provide social support and information and to foster advocacy in a positive manner. Parent support groups may help parents deal with the issues they are facing following a diagnosis, enable them to feel less isolated and have better access to information.[175, 225, 226] When parents receive support from their families and the community, caregiving stress may be relieved.

In Singapore, more formalised psycho-emotional and financial support for families is often provided through social workers based in clinics, hospitals, Voluntary Welfare Organisations (VWO) or Family Service Centres (FSC). Whilst these services do not cater exclusively to children with ASD, the professionals (social workers, or counsellors) would be able to direct them to appropriate services within the community (*See Appendix C)*.

D Parents and caregivers should be encouraged to discuss the need for practical emotional support. This enables information to be provided, referrals made and support services made available.

Grade D, Level 3

Parent education

Parent education is the process of systematically providing parents and other primary caregivers with specific knowledge and child-rearing skills to promote their children's development and competence.[227]

For parents of young children newly diagnosed with ASD, parent education and skills training programme results in significant improvements in parental mental health and adjustment.[228] Parent education has been found to work in: i) improving the social and communication skills of the children; and ii) producing a positive effect on children's social and communication behaviour, parental performance and parent-child interactions.[229, 230]

A Parents and caregivers of pre-school children with ASD are recommended to attend parent education programmes.

Grade A, Level 1+

Transition planning and educational placement

When children with ASD reach school-going age, appropriate school placement is often a priority. Educational placement should be determined in consultation with appropriate professionals such as developmental paediatricians, educational child psychologists, teachers and therapists who provide intervention for the child.

In Singapore, there is a variety of educational options for children with ASD. These range from full inclusion in mainstream, to special education (SPED) schools offering mainstream or specialised curriculum. As the diversity of provisions evolves with time, parents and caregivers should be provided with comprehensive current information about the different types of educational placements available so that they can make informed decisions. Information about local schools can be found at the following websites:

a) Mainstream schools :
http://app.sis.moe.gov.sg/schinfo/index.asp

b) Special education (SPED) schools:
http://www.moe.gov.sg/education/special-education/

GPP Parents and caregivers are recommended to consult appropriate professionals when considering educational placement for their child with ASD, e.g. child and educational psychologists who are informed of the special educational provisions in Singapore.

GPP

Transition planning from preschool settings to primary or SPED schools can result in quicker and more successful adjustments, leading to less disruption to teaching and learning. Effective transition planning requires collaboration amongst parents, caregivers and professionals. This involves teaching relevant skills to the child to function as independently as possible in the new setting, as well as assisting the professionals, teachers and staff in the new educational setting to understand the child's needs. Involving peers in the transition support process often leads to positive peer relationships in school.[231-233]

D Parents and caregivers are recommended to actively collaborate with professionals and teachers in preparing the child with ASD for the new educational setting, as well as modifying the new setting to accommodate the needs of the child.

Grade D, Level 4

Students with ASD attending mainstream schools may require special educational accommodation and support such as provision of explicit directions, specific curriculum or testing accommodations. Decisions on provisions and accommodations should be made in consultation with school personnel. Parents and teachers should seek input from relevant professionals (psychologists or therapists who provided intervention) to ascertain the individual child's specific educational needs.

GPP Parents and caregivers should be encouraged to give consent for information about special educational needs to be shared with school personnel for better planning of intervention and support.

GPP

11 Management: Pharmacological treatment

In pre-school children with ASD, management of mental health and behaviour issues should be multi-modal and addressed in a multi-disciplinary setting. Management of the environment, behavioural and psychological strategies should be considered together with pharmacotherapy as complementary aspects of a complete management plan for pre-school children with ASD. Treatment follows a contextual and functional analysis of behaviour, where attention must be given to the child's language ability and developmental level. The child's developmental level may be affected by medical disorders and life events.[234]

ASD cannot be cured with medication but pharmacological agents may be efficacious in treating dysfunctional behavioural symptoms that interfere with rehabilitative efforts and cause impairment or distress to the child with ASD.[235] Examples of mental health and dysfunctional behavioural symptoms include aggressive and self-injurious behaviour, anxiety, depression, tics, obsessive-compulsive behaviours, hyperactivity and sleep disturbances.

Pharmacological management of mental health disorders and dysfunctional behaviours in ASD should only be undertaken by doctors with appropriate training in mental health. Doctors who prescribe more than one medication should be vigilant about the possibility of drug interactions and monitor for possible side effects.

D Pre-school children with ASD are best managed by a multi-modal approach.

Grade D, Level 4

D Pharmacological treatment does not cure ASD. It may be considered when specific indications are present, such as aggressive and self-injurious behaviour, anxiety, depression, tics, obsessive-compulsive behaviours, hyperactivity and sleep disturbances.

Grade D, Level 4

D Pharmacological treatment should be given by doctors with appropriate training in mental health.

Grade D, Level 4

Pharmacological agents used in children with ASD include:

a) Tricyclic Antidepressants
b) Selective Serotonin Reuptake Inhibitors (SSRI)
c) Conventional anti-psychotic medication
d) Atypical anti-psychotics
e) Stimulant medication
f) Others

Available literature on the efficacy of pharmacological treatment for children with ASD was mostly based on those *over* 7 years old and adolescents. Recommendations in this CPG may not always be directly applicable to *pre-school* children with ASD.

Table 1 A list of pharmacological agents used for various dysfunctional behavioural issues in ASD *

	Repetitive, stereotyped behaviour	Anxiety	Aggression, Irritability, Self-injury	Hyperactivity Inattention	Sleep disturbances
Clomipramine	B	B			
Fluvoxamine @	D				
Fluoxetine	B				
Haloperidol			B		
Risperidone			A		
Olanzapine			D		
Methylphenidate				A	
Atomoxetine				D	
Melatonin					**B**

* Letters A to D refer to grading of Workgroup;
@ used mainly in adults with limited evidence in children

11.1 Tricyclic antidepressants

Tricyclic antidepressants block presynaptic reuptake of norepinephrine and serotonin to varying degrees. While the tricyclic antidepressants were the drugs of choice for management of depression in the 1980s, their nonselective action on cholinergic, histaminergic, and presynaptic adrenergic receptors have resulted in adverse effects. Clomipramine is a tricyclic antidepressant that may reduce irritability and stereotypical behaviour in children with autism. In a double-blind comparison study, clomipramine was shown to be superior to placebo and desipramine in improving autistic symptoms, anger, compulsive and ritualized behaviour in children aged 6 to 18 years old.[236] Children and adults who were given clomipramine and haloperidol demonstrated comparable improvements in irritability and stereotypy.[237, 238] However, clomipramine was poorly tolerated and associated with serious, untoward effects.[237, 239]

B Clomipramine may be considered for reducing irritability and stereotypical behaviour in children with ASD. Monitoring for tolerance and side-effects to clomipramine is recommended.

Grade B, Level 1+

11.2 Selective serotonin re-uptake inhibitors (SSRI)

Selective Serotonin Reuptake Inhibitors increase the extracellular level of the neurotransmitter serotonin by inhibiting reuptake into the presynaptic cell, increasing the level of serotonin available to bind to the postsynaptic receptor. They are typically used in the management of depression, anxiety and obsessive-compulsive disorders. Selective serotonin re-uptake inhibitors include fluvoxamine, fluoxetine, citalopram, escitalopram and sertraline.

Fluvoxamine was efficacious in improving repetitive thought patterns, maladaptive behaviour and repetitive language in a randomized controlled trial of adults with autistic disorders. When fluvoxamine was administered to children and adolescents with pervasive developmental disorders, the medication had limited efficacy and the children tolerated it poorly.[240-244]

D Fluvoxamine may be considered for repetitive thought and maladaptive behaviour but should be used with caution in children with ASD because of limited efficacy and poor tolerance.

Grade D, Level 3

Fluoxetine has been examined in a placebo-controlled crossover trial in children and adolescents with ASD and found to result in significant reduction in repetitive behaviour as compared to placebo, with no difference in side effects.[245] In an open-label study of fluoxetine in ASD children aged 2 to 8 years, improvements were evident in the behavioural, language, cognitive, affective and social domains. However, side effects were reported, including hyperactivity, agitation, lethargy, rash and diarrhea.[246] Two further studies conducted in older children and adults reported overall improvement in behaviour.[247, 248]

B Fluoxetine may be considered for the reduction of repetitive behaviours in children and adolescents with ASD. Monitoring for the side effects of fluoxetine is recommended.

Grade B, Level 1+

There is insufficient evidence for a recommendation regarding the use of citalopram,[249] escitalopram[250] and sertraline[251-253] for children with ASD.

11.3 Typical anti-psychotics: Haloperidol

Typical anti-psychotics (sometimes referred to as first generation anti-psychotics, conventional anti-psychotics, or major tranquilizers) are a class of anti-psychotic drugs first developed in the 1950s and used to treat psychosis. Typical anti-psychotics may also be used for the treatment of acute mania, agitation, aggression, and other conditions. The therapeutic actions of typical anti-psychotics lie in their antagonism of dopamine receptors, particularly the D_2 receptors. They may produce extra-pyramidal symptoms, such as Parkinsonism, dystonia, and tardive dyskinesia, as well as increased serum prolactin concentration.

Haloperidol is one of the most studied typical anti-psychotics in the management of autistic spectrum disorders. Two double-blind placebo-controlled cross-over trials concluded that the use of

haloperidol in children with ASD significantly reduced maladaptive behaviour. However, above therapeutic doses, haloperidol was associated with significant side effects, including excessive sedation, acute dystonic reactions and increased irritability. The side effects of haloperidol can be minimized at therapeutic doses through careful monitoring.[254-258]

B Haloperidol may be considered in the management of temper tantrums, aggression, hyperactivity, withdrawal and stereotypical behaviour in children with ASD, but careful monitoring of side effects is required.

Grade B, Level 1+

11.4 Atypical anti-psychotics

Atypical anti-psychotics are also known as second-generation anti-psychotics. They may be used for treatment of psychotic conditions, mania, agitation, aggression and other conditions. Their therapeutic action is characterized by lower D_2 antagonism with a broader spectrum of pharmacologic properties, including 5-HT_{2A} antagonism. Thus, the atypical anti-psychotics have a reduced propensity to produce extra-pyramidal symptoms, less prolactin elevation and a wider spectrum of therapeutic efficacy. However, second-generation anti-psychotic medications have recently been associated with potential adverse metabolic effects, such as weight gain, insulin resistance, dyslipidaemia and hyperglycemia.[259, 260]

A Atypical (second-generation) anti-psychotic medications are associated with potentially adverse metabolic effects, such as weight gain, insulin resistance, dyslipidaemia and hyperglycemia. Taking a thorough medical history and monitoring of body weight and blood sugar levels is recommended when atypical anti-psychotic medications are administered.

Grade A, Level 1++

11.4.1 Risperidone

Two large multi-centre randomized controlled trials concluded that risperidone improved irritability, hyperactivity and stereotypic behaviours when used as short-term management in children with ASD who were over 5 years old.[261, 262] The Research Units on Pediatric Psycho-pharmacology (RUPP) Autism Network showed that

there was high efficacy and good tolerability when risperidone was used for intermediate-length treatment of autistic children who displayed tantrums, aggression and self-injurious behaviour.[263] In terms of the core symptom domains of autism, the RUPP Autism Network demonstrated that the use of risperidone in children with autism resulted in significant improvement in restricted, repetitive and stereotypic behaviours, but did not significantly change the deficits in social interaction and communication skills.[264]

A Risperidone is recommended for the management of irritability, hyperactivity and stereotypic behaviour when used as short term treatment for children with ASD.

Grade A, Level 1++

11.4.2 Olanzapine

In a small case series, olanzapine was reported to significantly improve overall symptoms of autism including motor restlessness, social relatedness, affectional reactions, sensory responses, language usage, self-injurious behaviour, aggression, irritability, anxiety and depressive symptoms when given to children, adolescents and adults with ASD.[265] In an open pilot study of individuals with ASD from 7.8 to 21 years, 5 of 6 subjects in the olanzapine group and 3 of 6 in the haloperidol group were rated as responders.[266] An open-label study of olanzapine in 25 children with PDD found that 3 had improved CGI scores, including improvements in hyperactivity, excessive speech and irritability.[267] A small double-blind placebo-controlled study of olanzapine in children and adolescents concluded that it improved global functioning of PDDs.[268] Weight gain was shown to be the most prominent adverse effect of olanzapine in 2 studies reported. [265, 268]

D Olanzapine may be considered in the management of motor restlessness, self-injurious behaviour, aggression and irritability in children with ASD.

Grade D, Level 3

A Olanzapine administered to children with ASD may result in significant weight gain and healthcare professionals should monitor the child's weight closely.

Grade A, Level 1+

11.4.3 Quetiapine, Ziprasidone, Aripiprazole and Clozapine

There is insufficient evidence for a recommendation regarding the use of quetiapine,[269-272] ziprasidone,[273, 274] aripiprazole[275-277] and clozapine[278-281] for children with ASD.

11.5 Stimulant medication: Methylphenidate

Stimulant medication has been found to be an effective treatment strategy in children and youth with attention deficit hyperactivity disorder. In Singapore, methylphenidate is the most commonly used stimulant medication for attention deficit hyperactivity disorder. It is a potent central nervous system stimulant derived from amphetamine and is thought to exert its effect by enhancing dopaminergic transmission in the brain.

A large multi-centre randomized controlled crossover trial of methylphenidate in children 5 to 14 years old concluded that methylphenidate was often efficacious in treating hyperactivity associated with PDD, although the magnitude of response was often less than that seen in typically developing children with attention deficit hyperactivity disorder.[282] In the trial, adverse effects were more frequently seen in children with PDD than in those without.[282] In a small trial, 8 of 13 children (aged 5.6- 11.2 years) with autism and symptoms of attention deficit hyperactivity disorder had a 50% decrease in Conner's Hyperactivity Index.[283] Another small randomized trial of children aged 7-11 years with autistic disorder treated with methylphenidate found that there was significant improvement in irritability and hyperactivity.[284] Adverse effects such as irritability and social withdrawal were common in those treated with methylphenidate.[283]

A Methylphenidate may be considered for treating hyperactivity in children with ASD, although the magnitude of response is often less than that seen in typically developing children with attention deficit hyperactivity disorder.

Grade A, Level 1++

GPP Pre-school children with ASD receiving methylphenidate should be monitored for adverse effects.

GPP

11.6 Other medications

11.6.1 Alpha-2 adrenergic agonist

Alpha-2 adrenergic agents have been used in the management of hypertension and attention deficit hyperactivity disorder. The alpha-2 adrenergic agonists used in children with ASD are clonidine and guanfacine.

There is insufficient evidence for a recommendation regarding use of clonidine[285, 286] in pre-school children with ASD. Studies suggest that Guanfacine[287, 288] is promising in management of hyperactivity in children with ASD but is associated with side effects such as irritabioity, sedation, sleep disturbance and constipation

11.6.2 Anti-convulsant Medication

Some anti-convulsant medications such as divalproex, lithium and oxcarbazepine have been used in the management of mood disorders, impulsivity and aggression in general.

There is insufficient evidence for a recommendation regarding use of divalproex sodium,[289-291] lithium,[292,293] and oxcarbazepine[294] in children with ASD.

11.6.3 Atomoxetine

Atomoxetine is a non-stimulant drug approved for the treatment of attention-deficit hyperactivity disorder. It is a selective nor-epinephrine reuptake inhibitor. Several retrospective and open-label trials reported that atomoxetine improved symptoms of attention deficit hyperactivity disorder in children and adolescents with ASD.[295, 296] A small double-blind placebo-controlled cross-over trial of 16 children aged 5 to 15 years concluded that atomoxetine improved hyperactivity but not inattention.[297] Although one author found that atomoxetine was associated with gastro-intestinal side effects, fatigue and appetite change,[298] others reported that the adverse events were tolerable.[297]

D Atomoxetine may be considered for managing attention deficit hyperactivity disorder-like symptoms in children with ASD.

Grade D, Level 3

11.6.4 Glutamatergic antagonist

Glutamatergic antagonists are amantadine and memantine. Amantadine hydrochloride is a noncompetitive N-methyl-D-aspartate antagonist routinely used for treatment of influenza, herpes zoster and Parkinson disease. Memantine is a glutamatergic antagonist used in treating Alzheimer's disease.

There is insufficient evidence for a recommendation regarding use of amantadine[299] in children with ASD. Studies suggest memantine[300-302] shows promise in manageing symptoms of hyperactivity and inattention in children with ASD.

11.6.5 Melatonin

Melatonin is a naturally occurring hormone that is important in the regulation of the circadian rhythms of biological functions, including sleep. Two randomized controlled[303, 304] and three open-label trials[305-307] reported on the usefulness of melatonin for children and adolescents with ASD who experience sleep disorders and poor sleep maintenance.

B Melatonin may be considered in the management of the disturbed sleep patterns of children with ASD.

Grade B, Level 1+

11.6.6 Opiate Antagonist: Naltrexone

Several double-blind placebo-controlled crossover trials of naltrexone in young (2.9 to 8.3 years) children with autism concluded that naltrexone reduced irritability and hyperactivity in the children.[308-310] However, in studies investigating naltrexone on communication skills and learning in children with autism,[311-314] there was no effect on social behaviour, communication, stereotypic behaviour[308, 311] and discrimination learning.[310]

12 Management: Complementary alternative therapies

Introduction

Complementary and alternative therapies refer to a wide range of interventions that augment mainstream interventions. Use of complementary and alternative therapies (CAT) is prevalent, more so among children with ASD than the general paediatric population, and likely to increase.[315-318] This may be due to the pervasive nature of ASD, easy access to health information, claims of cure by practitioners of alternative therapies as well as the long time-frame for improvement to be seen when mainstream intervention is practised.

Intervention should be based on evidence from well-designed research and be part of standard practice. While sufficient intensity (duration) of intervention is desirable (*refer to chapter 9),* it is equally important to ensure quality of intervention by achieving a balance of various interventions that address the core deficits of ASD. Parents and caregivers should be encouraged not to replace traditional, mainstream interventions with CAT. Decisions to use CAT must take into consideration several factors, including:

a. How the CAT adds value to an existing mainstream programme;
b. Implications on investing limited resources (i.e., time, money and manpower) on interventions that may not produce desired results and detract caregivers from evidence-based interventions;
c. The potential for harm, disability or medical illness, especially in the young growing child who has vulnerable neurological and physiological systems.

GPP Parents and caregivers should not replace mainstream interventions for pre-school children with ASD with complementary and alternative therapies.

GPP

Because of the plethora of CAT used in children with ASD, it is neither practical nor feasible to review evidence for all CAT and this guideline only reviewed therapies/interventions frequently discussed in clinical settings or associated with extensive research. Since research into CAT is ongoing, this workgroup reviewed evidence that was available up to the time of publication of the guideline. In general,

evidence for the efficacy of CAT remained limited with none meeting criteria for effective intervention. When professionals discuss the use of CAT with parents of children with ASD, it is important to explain potential harms and benefits associated with CAT. The workgroup committee recommends that the decision to use CAT be guided by evidence of its efficacy and safety in scientific studies employing adequate research design. Therefore, healthcare professionals should keep themselves updated on developments in the field of CAT.

GPP Healthcare professionals caring for pre-school children with ASD should advise and counsel parents and caregivers about relevant, safe and effective health services and therapies regardless of whether the therapies are mainstream or CAT.[319]

GPP

Complementary alternative therapies (CAT) were divided into:

12.1 CAT with insufficient or conflicting evidence of efficacy;
12.2 CAT with sufficient evidence that the therapy was ineffective;
12.3 CAT with potential for harm

12.1 CAT with insufficient, conflicting or inconclusive evidence

These complementary alternative therapies (CAT) had insufficient, conflicting or inconclusive evidence for efficacy at the time of writing. Until further evidence of efficacy becomes available, healthcare professionals caring for pre-school children with ASD should exercise prudence when advising parents or caregivers who are keen to consider using these CATs.

The following CATs are **not recommended** for pre-school children with ASD because of insufficient, conflicting or inconclusive evidence:

- Amino acid supplementation
- Animal-assisted therapy
- Behavioural optometry
- Expressive psychotherapy
- Gluten-free and/or casein-free diet
- Sound therapies (Samonas Sound Therapy and the Listening Programme)

- Massage and other sensory-based interventions
- Music therapy
- Omega-3 fatty acid (O3FA) supplementation

12.1.1 Amino acid supplementation

Amino acid supplementation in children with ASD was based on the role of amino acids in neuro-transmission and metabolism.[320] The efficacy of amino acid supplementation in children with ASD has not been rigorously investigated in large controlled trials. In an eight-week small double-blinded study of children with ASD, a daily dose of 800mg carnosine compared to placebo resulted in improvement in the Gillian Autism Rating Scale and Receptive One-Word Picture Vocabulary test, although the mechanism of action was ill understood.[321] High doses of amino acids (especially methionine, isoleucine, threonine and tryptophan) administered to children may result in nausea, appetite suppression and liver dysfunction.[322] The upper limit of amino acid intake is not established.

D High dose amino acid supplementation is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy.

Grade D, Level 3

12.1.2 Animal-assisted therapy

Animal-assisted therapy refers to interventions in which animals, such as dolphins, horses (hippotherapy) or dogs, are employed in the support of individuals with ASD.[323-327] Animals are used in a variety of ways ranging from being a daily life assistant to a therapeutic tool. Evidence for efficacy of animal-assisted therapy for children with ASD was insufficient.[326] Employment of animals raised concerns of harm to the child and/or animal when an initially tame animal may be provoked by a volatile child, when a child may unexpectedly react aggressively to the animal or when there is zoonotic disease transmission to the child from an animal.[328]

D Animal-assisted therapy is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy.

Grade D, Level 3

12.1.3 Behavioural optometry

Behavioural optometry employs behavioural vision therapy to train visual processing skills, visual motor integration and learning efficiency. Studies of behavioural optometry in children with ASD were largely uncontrolled, few in number and produced inconsistent results.[329, 330] The conclusion of systematic reviews as well as the consensus of ophthalmologists, orthoptists and pediatricians was that there was a lack of evidence for the effectiveness of behavioural optometry in remediation of learning problems associated with ASD.[331-336]

D Behavioural optometry is not recommended in the routine management of children with ASD because of conflicting evidence.

Grade D, Level 3

12.1.4 Expressive psychotherapy

Expressive psychotherapy includes art therapy, play therapy, drama therapy and sand-tray therapy.[337, 338] ASD is not associated with psychodynamic factors or poor parenting (*refer to chapter 7*); therefore, there is no biological basis for the use of expressive psychotherapy as a form of therapy for ASD.

D Expressive psychotherapy is not recommended in the routine management of children with ASD because of insufficient evidence for efficacy.

Grade D, Level 3

12.1.5 Gluten-free, casein-free (GFCF) diet

Gluten-free, casein-free (GFCF) diets for children with ASD was based on the hypothesis that children with autism had abnormal intestinal digestive ability and permeability, leading to excessive central opioid activity and behavioural, communicative, social and cognitive difficulties.[339-347] Immune dysfunction resulting in allergy to gluten and casein was implicated.[342] These hypotheses remain unsubstantiated by rigorous scientific data.[348] Clinical trials with opiate antagonists were not consistently beneficial.[308, 309]

Systematic reviews had studied the effectiveness of GFCF diets for treating ASD.[144,349,350] In a Cochrane review of 2 randomised controlled trials that studied the effectiveness of GFCF diets in children with ASD, results were contradictory and meta-analysis could not be performed because of the heterogeneity of data.[347,351] The reviewers concluded that there was insufficient evidence to recommend the GFCF diet in ASD.

There are practical difficulties in keeping strictly to a GFCF diet, including difficulty in ensuring compliance as well as the extra cost and preparation time required. Furthermore, there are concerns of dietary restriction in children who may already have rigidity and sensory limitations in feeding *(refer to chapter 9*). One study found that compared to matched controls, children with autism on strict GFCF diets showed a trend towards increased prevalence of essential amino acid deficiency and lower plasma levels of essential amino acids including the neurotransmitter precursors tyrosine and tryptophan.[352] In another study, children with autism on GFCF diets were shown to have lower bone cortical thickness compared to controls.[353] Parents and/or caregivers must ensure that the pre-school child receives adequate calcium, vitamin D and protein intake for optimal growth.

D Gluten-free casein-free diets are not recommended in the routine management of children with ASD because of conflicting evidence.

Grade D, Level 3

12.1.6 Sound therapies (Samonas or The Listening Program®)

Sound therapy may be provided as Auditory Integration Therapy (*refer to 12.3.4 for Auditory Integration Therapy),* Samonas or The Listening Program®. Samonas is based on listening to CD classical music. It was reported to improve psychological and physiological conditions, such as hearing, learning difficulties, voice problems and behaviour disturbances. Another form of listening therapy called the Listening Programme consisted of reproduced filtered music available in CDs. A Cochrane review in 2004 found no trials that assessed Samonas or The Listening Programme in children with ASD.[354]

D Sound therapies (either as Samonas or the Listening Programme®) are not recommended in the routine management of children with ASD because of insufficient evidence for efficacy.

Grade D, Level 3

12.1.7 Massage and other sensory-based interventions

Massage is the passive application of controlled sensory stimulation. It includes applying deep pressure, tension, motion or vibration to the skin, muscles or other soft tissues of the body. Other sensory-based interventions include brushing and rubbing of the body, touch therapy, deep pressure and compression of joints. Use of massage was suggested as a means to reduce social and attentive behaviour issues, anxiety issues, sleep and bowel movement problems in children with ASD.[355-364] However, these studies had weak methodology and evidence was inconclusive.

D Massage and other sensory-based interventions are not recommended in the routine management of children with ASD because of insufficient evidence for efficacy.

Grade D, Level 3

12.1.8 Music therapy

Music therapy is a specific intervention using music communication and expression, including free and structured improvisation, songs and listening to music. This is based on the premise that musical interaction and improvisation may be considered a type of non-verbal and pre-verbal language training.[365, 366]

Systematic reviews of music therapy for ASD produced contradictory conclusions. A meta-analysis concluded that all music intervention was effective for children and adolescents with autism.[367] While one review found a generally positive effect of music therapy,[368] another review was unable to identify possibly relevant studies of music therapy and concluded that its effects were unclear.[369] In a Cochrane review of 3 studies that examined the short-term effect of brief music therapy for autistic children, the reviewers concluded that music therapy was superior to placebo with respect to verbal and gestural communication, but had insignificant effect on behavioural problems.[370] Of note, the reportedly positive effect of music therapy was based on using highly structured receptive techniques. This may

have limited clinical applicability because in practice, music therapy tends to be associated with less structure and the use of improvisational techniques. When applying the results of the review to practice, it is important to note that application of music therapy require specialised academic and clinical training. In a recent small randomized controlled trial that used improvisational techniques, music therapy was found beneficial in promoting the social, emotional and motivational development of children with autism.[371, 372]

D Music therapy is not recommended in the routine management of children with ASD because of inconclusive evidence.

Grade D, Level 3

12.1.9 Omega-3 fatty acid (O3FA) supplementation

The result of omega-3 fatty acid (O3FA) supplementation in ASD individuals was conflicting. While observational data suggested that levels of O3FA in ASD individuals was lower compared to controls and may be improved through supplementation,[373-376] others failed to detect O3FA deficiency or demonstrate benefits of O3FA supplementation.[377,378] A systematic review identified only 1 randomized controlled trial and concluded that there was insufficient evidence to determine the effectiveness and safety of O3FA supplementation in children with ASD.[379]

Adverse effects reported with O3FA supplementation included gastro-intestinal complaints (diarrhea, heartburn, indigestion, and abdominal bloating), fever, increased hyperactivity and behavioural problems.[379] At high doses, drug interactions may occur, such as with anti-coagulant and anti-hypertensive medication.[264] The advice of the Australian National Health and Medical Research is that the upper limit of O3FA intake in children, adolescents and adults should not exceed 3 grams per day.

D High dose omega-3 fatty acid supplementation is not recommended in the routine management of children with ASD because of inconclusive evidence for efficacy.

Grade D, Level 3

12.2 CAT with sufficient evidence that the therapy was ineffective

The following complementary alternative therapies are **not recommended** in the routine management of children with ASD because of evidence that they are ineffective:

- Dimethylglycine supplementation
- Patterning therapy without masking

12.2.1 Dimethylglycine supplementation

Dimethylglycine (DMG) is closely related to the neurotransmitter glycine with the potential to cross the blood-brain barrier and influence the overall balance of inhibitory versus excitatory neurotransmitters. Evidence for the effects of DMG supplementation in ASD comes from anecdoctal reports and case series.[380, 381] In two small double-blind placebo-controlled trials of DMG, no improvement was reported in the treatment groups as compared to controls.[382, 383] One child who was given DMG supplements was reported by the parents to have been more 'edgy'.[382, 383]

D Dimethylglycine supplementation is not recommended for pre-school children with ASD because it is ineffective.

Grade D, Level 3

12.2.2 Patterning therapy without masking

Patterning therapies constitute a class of interventions based on the belief that autism is one of many disorders caused by some form of brain injury. It includes the Doman-Delecato or Glenn Doman programme, autism rehabilitation therapy, psychomotor patterning and developmental reflexive rehabilitation.[384-387] Patterning therapy involves a series of bodily exercises and other activities designed to "rewire" the brain in individuals with autism and other disorders.[262, 388] In a full treatment programme, exercises are combined with sensory stimulation, breathing exercises termed "masking" and a programme of restriction and facilitation designed to promote hemispheric dominance.[389]

A review of patterning therapies by professional organizations[384-387] since the 1960s, including the American Academy for Cerebral Palsy, American Academy of Neurology and American Academy of Pediatrics[384-387] concluded that "this treatment is based on an outmoded and oversimplified theory of brain development. Current information does not support the claims of proponents that this treatment is efficacious, and its use continues to be unwarranted". There are concerns of harm for patterning *with* masking, which is discussed separately in section 12.3.3.

D Patterning without masking is not recommended for pre-school children with ASD because it is ineffective.

Grade D, Level 4

12.3 CAT with potential for harm

Potential for harm was evaluated in terms of the risk of death, disability and medical or psychological disorders. The impact of interventions was considered in the context of the child's growth and development, especially during the vulnerable pre-school years. Healthcare professionals caring for pre-school children with ASD should advise parents and caregivers to avoid using any of these CATs in view of the potential for harm.

The following complementary alternative therapies are **not recommended** in pre-school children with ASD because of potential for harm or adverse effects:

- Acupuncture
- Antibiotics and Anti-yeast medication
- Ascorbic acid (vitamin C) supplementation
- Auditory Integration Therapy
- Chelation therapy
- Chiropractic
- Cranio-sacral therapy
- Digestive enzymes
- Facilitated Communication
- Folate supplementation
- Holding Therapy
- Hyperbaric Oxygen Therapy
- Intravenous Immunoglobulin therapy
- Patterning with masking

- Secretin therapy
- Vitamin B6 – Magnesium supplementation
- Weighted vests
- Zinc supplementation

12.3.1 Acupuncture

An integral part of traditional Chinese medicine, acupuncture involves the insertion of metallic needle(s) into the skin for 3-5mm. It is sometimes used in combination with moxibustion and electrical stimulation. Methods of acupuncture in ASD include electro-acupuncture, "Jin's Sanzhen" method, seven-star needle stimulation and scalp acupuncture.

A Cochrane systematic review of acupuncture for ASD is ongoing. There was insufficient evidence for efficacy due to a paucity of studies and poor quality of research.[390] It was difficult to relate the beneficial outcomes reported in children with ASD to acupuncture alone because of poor study design or publication bias.[390, 391] Adverse effects of acupuncture are rare when it is appropriately administered. However, cases of infection (from inadequate needle sterilization), haemorrhage, needling pain, organ puncture and symptom aggravation had been reported following acupuncture.[392-395]

D Acupuncture is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for harm†.

***†Grade D, Level 3**

12.3.2 Antibiotics and anti-yeast medications

Intestinal dysbiosis and immune dysregulation in children with ASD was suggested to contribute to autism symptoms. However, intestinal candidial over-growth was not observed during endoscopy in children with ASD.[109] Rather, an overgrowth of yeast and pathogenic bacteria may result from frequent prolonged courses of antibiotic treatment. Evidence on the efficacy of vancomycin in children with ASD was inconclusive.[396] There are serious adverse effects associated with indiscriminate use of antibiotics, including the emergence of antibiotic-resistant bacteria such as vancomycin–resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus spp.* Chronic use of anti-fungal therapy is associated with hepatotoxicity

and exfoliative dermatitis, while nystatin is associated with diarrhoea.[397]

D Antibiotic and anti-yeast therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for adverse effects†.

***†Grade D, Level 3**

12.3.3 Ascorbic Acid (Vitamin C) supplementation

The pharmacologic effect of ascorbic acid was postulated to be similar to that of conventional neuroleptics, especially blockade of dopamine receptors. A double blind, placebo-controlled trial exploring the effects of ascorbic acid supplementation in 18 children in residential treatment reported a reduction of autistic symptoms in selected individuals but findings were preliminary.[398] Adverse effects of excessive ascorbic acid consumption include osmotic diarrhoea, nausea and abdominal cramps. Although other adverse effects, such as kidney stone formation, excess iron absorption, reduced vitamin B_{12} and copper levels, increased oxygen demand, systemic conditioning, pro-oxidant effects, dental enamel erosion, or delayed-type allergic response had been observed before, *in vivo* data did not demonstrate a clear causal relationship.[250] The National Academy of Sciences defined upper tolerable limits of ascorbic acid as 400 mg/day in children 1-3 years old and 650 mg/day in children 4-8 years old respectively.[250]

D High dose ascorbic acid supplementation is not recommended for ASD because of insufficient evidence for efficacy* and the potential for adverse effects†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.4 Auditory Integration Therapy (AIT)
(Refer to 12.1.6)

Auditory Integration Therapy (AIT) includes the "Berard" method and "Tomatis and Clarke" method. An AIT programme consists of listening to music that has been computer-modified to remove frequencies to which the listener demonstrates hypersensitivity and reduce the predictability of auditory patterns. A Cochrane review concluded that studies of auditory integration therapy showed

significant methodological weaknesses and meta-analysis was not possible due to very high level of heterogeneity and unusable presentation of data.[354] There was concern with quality control of the equipment and potentially unsafe sound levels produced.[399] Hearing damage due to the volume and sound pressure used during treatment was reported.[60, 400]

A&D Auditory Integration Therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for damage to hearing†.

***Grade A, Level 1++**
†Grade D, Level 3

12.3.5 Chelation therapy

Chelation therapy, through intravenous, subcutaneous, oral and topical routes, was proposed as a solution to address childhood exposure to environmental neurotoxins, such as mercury and lead, that had been suggested as a possible cause for ASD (*refer to Chapter 7*). There were no studies showing that mercury exposure was the cause for the development of ASD or that children with ASD had greater exposure to mercury than unaffected children. There was no evidence confirming that the chelation of heavy metals would improve the developmental skills of children with ASD. Furthermore, chelation therapy is known to be associated with adverse effects such as hepatotoxicity, nephrotoxicity, Stevens-Johnson syndrome, hypocalcemia and death.[397, 401-404] In 2005, a 5-year old child with autism was reported to have died during chelation therapy.[405]

D Chelation therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for harm including death†.

***†Grade D, Level 3**

12.3.6 Chiropractic

Chiropractic involves spinal adjustment, manual therapy on other joints, soft-tissue manipulation and sometimes exercises, massage and lifestyle counselling to restore health.[406] Results of research on the efficacy of chiropractic treatment was conflicting.[407, 408] There is little evidence to support use of chiropractic in ASD.[409]

Chiropractic care is generally regarded as safe when used appropriately. However, there were reports of adverse effects associated with spinal manipulation,[410] including subarachnoid haemorrhage, paraplegia, headache and delayed diagnosis of neuroblastoma.[411] Chiropractors who occasionally employed diagnostic imaging techniques such as X ray and CT scan may expose the child to risks of radiation exposure.[412, 413]

D Chiropractic is not recommended for children with ASD because of conflicting evidence of efficacy* and the potential for harm†.

***†Grade D, Level 3**

12.3.7 Cranio-sacral therapy

Cranio-sacral therapy is based on the theory that gentle manipulation of the spine, skull and related soft tissues restores dysfunction in the rhythmic fluctuations of the cerebro-spinal fluid, soft tissue and cranium. There was no study to show that cranio-sacral therapy was efficacious in ASD.[380, 414]

Side effects from cranio-sacral therapy had been reported, including depression, confusion, headaches, diplopia, vertigo, nausea, vomiting, loss of consciousness, trigeminal nerve damage, hypopituitarism, brainstem dysfunction and opisthotonus.[414]

D Cranio-sacral therapy is not recommended for children with ASD because of insufficient evidence for efficacy* and the potential for harm†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.8 Digestive enzymes

Use of digestive enzymes was based on the disproven theory that ASD is caused by intestinal dysfunction and opioid excess from exorphins (pre-opioid compounds). Digestive enzyme therapy was proposed as a way to remove exorphins from the body. No controlled trials were published regarding efficacy of digestive enzymes for treating ASD in children.[380, 397, 415] Digestive enzymes were associated with adverse effects in one study, including hyperactivity, aggression, diarrhoea and poor appetite.[415]

D Digestive enzyme therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for adverse effects†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.9 Facilitated communication

Facilitated communication is a technique' that involves a facilitator physically supporting the child's arm or hand to type or point at pictures, symbols, letters and/or words. Systematic reviews concluded that facilitated communication was not effective for children with ASD.[400, 416-418] The authenticity of facilitated communication outputs by ASD individuals had been questioned,[418-428] and concerns had been raised regarding the potential for abuse. For example, false reports pertaining to personal preferences, family relations and psychosocial health were made. False allegations of abuse led to legal, psychological and financial problems for affected families.[429-431] Information obtained through, or based on facilitated communication should not form the sole basis for making any diagnostic or treatment decisions for the pre-school child with ASD.[397, 400, 416, 417, 432, 433]

A&D Facilitated communication is not recommended for children with ASD because of lack of efficacy* and the potential for abuse†.

***Grade A, Level 1+**
†Grade D, Level 3

12.3.10 Folate supplementation

It was hypothesized that oxidative stress led to neuronal insult and regression seen in some children with autism.[434] Although some autistic individuals were observed to have decreased methylation capacity that improved with methylcobalamin and folinic acid treatment, metabolic changes were not correlated with clinical symptoms.[435-437] There was no evidence for the efficacy of folate supplementation in children with ASD. Excessive folate supplementation may mask vitamin B_{12} deficiency and result in unrecognized neurological damage. The National Academy of Sciences defined upper tolerable limits of folate from fortified foods or supplements as 300 µg/day for children 1-3 years old and 400 µg/day for children 4-8 years old respectively.[267]

D High dose folate supplementation is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for adverse effects†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.11 Holding therapy

Holding therapy evolved over the years and had been named variously as rebirthing, compression therapy, the "Evergreen model", rage-reduction, corrective attachment therapy, Coercive Restraint Therapy, hug therapy, holding time, cuddle time, gentle containment, holding-nurturing process, prolonged parent-child embrace therapy and attachment therapy.

Efficacy of Holding therapy in autism remains unsubstantiated by rigorous scientific evidence. The American Professional Society on the Abuse of Children (APSAC) Task Force report stated that "A central feature of many of these therapies is the use of psychological, physical, or aggressive means to provoke the child to catharsis, ventilation of rage, or other sorts of acute emotional discharge. To do this, a variety of coercive techniques are used… so they can be forced to engage in prolonged eye contact… Similar but less physically coercive approaches may involve holding the child and psychologically encouraging the child to vent anger toward her or his biological parent."[438] These methods are potentially abusive and resulted in tragic outcomes for children, including death.[439]

D Holding therapy is not recommended for children with ASD because of lack of efficacy* and the potential for harm, including death†.

***†Grade D, Level 3**

12.3.12 Hyperbaric oxygen therapy (HBOT)

Hyperbaric oxygen therapy (HBOT) was proposed as a way to increase the oxygen supply to the brain of individuals with autism, thereby reducing inflammation and mobilizing stem cells from human bone marrow to aid in neuroregeneration.[440,441] A multicentre randomized double-blind controlled trial concluded that HBOT may improve symptoms in children with ASD, but did not calculate the sample size of the primary outcome.[442-444] Reported adverse effects of

HBOT included ear barotrauma, pneumothorax, oxygen-induced convulsions, fire and explosions.[445]

D Hyperbaric oxygen therapy is not recommended for children with ASD because of insufficient evidence of efficacy* and the potential for harm†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.13 Intravenous immunoglobulin therapy

There is no evidence that ASD is related to brain/meningeal inflammation or caused by specific infectious agents (*refer to chapter 7*). In a double-blind, placebo-controlled trial of oral human immunoglobulin used for 12 weeks to treat gastro-intestinal dysfunction in children aged 2-17 years with autistic disorder, human immunoglobulin treatment was not found to be superior to placebo in reducing autistic symptoms.[128] Use of immunoglobulin may be associated with common side effects such as headache, nausea, malaise, fever, urticaria, arthralgia and myalgia. Less common but potentially fatal side effects include anaphylaxis, aseptic meningitis, acute renal failure, stroke, myocardial infarction and thrombotic complications.[446]

D Immunoglobulin therapy is not recommended for children with ASD because it is ineffective* and there is potential for adverse effects†.

***†Grade D, Level 3**

12.3.14 Patterning with masking

(Refer to 12.2.2 for Patterning therapy without masking)

Patterning with Masking aims to increase the carbon dioxide level in re-breathed air, so that the child with ASD would develop cerebral vasodilatation as a result of inhaling the carbon dioxide-rich air and indirectly promote oxygen delivery to the brain.[389] Inhaling re-breathed air that is carbon dioxide-rich but depleted of oxygen is potentially dangerous to the child. Long-term effects on the developing brains of young children are unknown.[384-387]

D Patterning with masking is not recommended for children with ASD because it is ineffective* and there is potential for harm to the child's developing brain†.

***†Grade D, Level 4**

12.3.15 Secretin therapy

Secretin is a hormone currently approved for the diagnostic evaluation of pancreatic and intestinal function. Use of intravenous secretin in children with ASD was based on anecdotal experience in 1998.[447] Extensive research over the past decade has since shown that secretin was ineffective for the treatment of ASD.[448-453] A Cochrane review in 2005 concluded that there was no evidence for the efficacy of secretin in the treatment of ASD, whether in single or multiple doses.[448] Adverse effects of secretin include increased tantrums, aggression, hyperactivity, raised liver function test, stomachache, emotional lability, fractures, seizures, vomiting, fever tachycardia and flushing.[448]

A&D Intravenous secretin is not recommended for children with ASD because it is ineffective* and there is potential for serious adverse effects†.

***Grade A, Level 1++**
†Grade D, Level 4

12.3.16 Vitamin B6 – Magnesium supplementation

A Cochrane systematic review included 3 small randomized controlled trials of vitamin B6-Magnesium in ASD but was unable to perform meta-analysis because of heterogeneity of data. Of the 3 trials, one reported improvement in verbal intelligence in the treatment group,[454] while the other 2 found no significant difference between treatment and placebo groups.[455,456] The reviewers were unable to recommend vitamin B6 and magnesium as treatment options for autism due to the small number of studies, poor methodological quality and small sample size.[457] Another study had similar methodological issues.[458] Whilst vitamin B6 and magnesium obtained from food sources had not been reported to cause adverse effects, high doses of vitamin B6 supplementation were associated with side effects, including peripheral neuropathy, vomiting, hypersensitivity to sound, irritability, depression, photosensitivity and enuresis.[235, 267, 294, 459]

D High dose vitamin B6 - magnesium supplementation is not recommended for children with ASD because of conflicting evidence* and the potential for adverse effects†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.17 Weighted vests

The wearing of a weighted vest or straps with evenly distributed weights, was used to reduce a range of problems, especially inattention and stereotypical behaviours. The weight prescribed and duration of use varied widely.[460] Evidence on efficacy of weighted vests on ASD was limited.[460] Wearing of a vest that includes weights beyond the prescribed weight limit and for a duration beyond the prescribed length of time may potentially affect the musculo-skeletal development of the growing child.[460]

D Wearing of weighted vests is not recommended for children with ASD because of insufficient evidence of efficacy* and potentially adverse effects on the developing spine†.

***Grade D, Level 3**
†Grade D, Level 4

12.3.18 Zinc supplementation

Zinc plays a role in the immune response, neurotransmitter production and anti-oxidant property. Various studies did not consistently prove that children with ASD are deficient in zinc.[461, 462,463] There were no controlled studies that examined the efficacy and safety of zinc supplementation for children with ASD.[464] Chronic intake of supplemental zinc resulted in immune suppression, a decrease in high-density lipoprotein cholesterol and lower copper status. Acute side effects of zinc supplementation included epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhoea and headache.[465]

D Zinc supplementation is not recommended for children with ASD because of insufficient evidence for efficacy* and potential for adverse effects†.

***†Grade D, level 4**

13 Clinical quality improvement

This CPG for Autism Spectrum Disorder in pre-school children was formulated to assist local practitioners in the areas of surveillance screening, early idenitification, referral, diagnosis and intervention. It aims to encourage a change in mindset and practice. The importance of equiping primary care doctors in early identification of ASD cannot be over-emphasised.

The following two clinical quality indicators in the areas of surveillance are important measures of Clinical Quality Improvement for care of children with ASD.

1. All professionals who deal with pre-school children, whether in health care services or early childhood education centres, should receive training on the “key signs" that suggest a diagnosis of ASD.

Clinical Quality Indicator
Training in 'key signs' of ASD and MCHAT provided through the College of Paediatric and Child Health, Singapore (Academy of Medicine, Singapore), and College of Family Physicians, Singapore, to primary care doctors (i.e. General practitioners, polyclinic doctors and private paediatricians).

To achieve
- 20% of all primary care doctors trained in year 1
- 40% of all primary care doctors trained in year 2
- 50% of all primary care doctors trained in year 3

2. Professionals should aim to identify ASD early. Early identification provides opportunity for early referral and intervention, so that the child with ASD may have improved functioning in later life.

Clinical Quality Indicator
Decreasing age at referral/diagnosis of ASD over the next 3 years.

14 Cost-effectiveness issues

The increase in the number of children diagnosed with ASD has resulted in a growing demand for current estimates of economic costs associated with ASD. In addition, children with ASD are more likely than others to have a number of medical conditions, resulting in the potential for greater use of health services.[466] No cost-effectiveness comparisons between different interventions for ASD appear to have been conducted.

Four recent studies reported consistent medical expenditure estimates for children with ASD in the US. On average, medical expenditures for children with ASD were 3-9 times greater than for those without because of increased costs for hospitalisations, medications, and out-patient clinic visits.[466-469] In addition, a US study[470] estimated that the average loss of annual income associated with having a child with ASD was 14% of annual income, suggesting significant burden for families.

Two cost-benefit studies of the early intensive behaviour intervention programme for young children in the US indicated that the implementation of early intervention for children with ASD would generate cost savings to the government, compared with no early intervention.[471,472] This was primarily due to a reduction in years of special education. These studies suggest that early intervention could improve functioning and quality of life for children with ASD as well as generate cost savings for the government.

Although results from other countries may not be generalised to the local context due to different health care systems and cost estimates, these studies add to our understanding of the health-related economic impact of ASD.

Annex A DSM-IV-TR and ICD-10 Diagnostic Criteria for Autism

DSM-IV-TR Criteria for Autistic Disorder[iv]

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 behaviors 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 others (e.g., 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 gesture 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

[iv] Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

3. Restricted, repetitive, and stereotyped patterns of behavior, interest, 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 (e.g., 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.

ICD-10 Criteria for Autism[v]

F84.0 Childhood Autism

A. Abnormal or impaired development is evident before the age of 3 years in at least one 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. A total of at least six symptoms from (1), (2) or (3) must be present, with at least two from (1) and at least one from each of (2) and (3):
   (1) Qualitative impairments in social interaction are manifested in at least two of the following areas:
      (a) Failure to adequately use eye-to-eye contact, facial expression, body postures, and gestures to regulate social interaction;
      (b) 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;
      (c) 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;
      (d) Lack of spontaneous seeking to share enjoyment, interests, or achievement with other people (e.g. a lack of showing, bringing, or pointing out to other people objects of interests to the individual).
   (2) Qualitative abnormalities communication as manifest in at least one of the following areas:
      (a) Delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);

[v] Reproduced from ICD-10 Classification of Mental and Behavioural Disorders – diagnostic criteria for research (1995). Geneva: World Health Organisation, 147-150.

(b) Relative failure to initiate or sustain conversational interchange (at whatever level of language skill is preset), in which there is reciprocal responsiveness to the communications of the other persons;
(c) Stereotyped and repetitive use of language or idiosyncratic use of words or phrases;
(d) Lack of varied spontaneous make-believe play or (when young) social imitative pay.

(3) Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities are manifested in at least one of the following:
(a) 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 though not in their content or focus;
(b) Apparently compulsive adherence to specific non-functional routines or rituals;
(c) Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole-body movements;
(d) Preoccupations with part-objects or non-functional elements of play materials (such as their odour, the feel of the surface, or the noise or vibration they generate).

C. The clinical picture is not attributable to other varieties of pervasive developmental disorders; specific disorder of receptive language (F80.2); mental retardation (F70-F72) with some associated emotional or behavioural disorders; schizophrenia (F20) of unusually early onset; and Rett's Syndrome (F84.12).

F84.1 Atypical Autism

A. Abnormal or impaired development is evident at or after the age of 3 years (criteria as for autism except for age of manifestation).
B. There are qualitative abnormalities in reciprocal social interaction or in communication, or restrictive, repetitive, and stereotyped patterns of behaviour, interests and activities. (Criteria as for autism except that it is unnecessary to meet the criteria for a number of areas of abnormalities.)
C. The disorder does not meet the criteria for autism (F84.0).

Autism may be atypical in either age of onset (F84.10) or symptomatology (F84.11): the two types are differentiated with a fifth character for research purposes. Syndromes that are typical in both respects should be coded F84.12.

F84.10 Atypicality in age of onset

A. The disorder does not meet the criterion A for autism (F84.0); that is abnormal or impaired development is evident only at or after age 3 years.
B. The disorder meets criteria B and C for autism (F84.0).

F84.11 Atypicality in symptomatology

A. The disorder meets criterion A for autism (F84.0); that is, presence of abnormal or impaired development before the age of three years.
B. There are qualitative abnormalities in reciprocal social interactions or in communication, or restricted, repetitive and stereotyped patterns of behaviour, interests, and activities. Criteria as for autism except that it is unnecessary to meet the criteria for a number of areas of abnormality).
C. The disorder meets criteria C for autism (F84.0).
D. The disorder does not fully meet criteria B for autism (F84.0).

F84.11 Atypicality in both age of onset and symptomatology

A. The disorder does not meet criterion A for autism (F84.0); that is, abnormal or impaired development is evident only at or after age 3 years.
B. There are qualitative abnormalities in reciprocal social interactions or in communication, or restricted, repetitive and stereotyped patterns of behaviour, interests, and activities. Criteria as for autism except that it is unnecessary to meet the criteria for a number of areas of abnormality).
C. The disorder meets criteria C for autism (F84.0).
D. The disorder does not fully meet criteria B for autism (F84.0).

Annex B Key signs for identification of children with ASD

(New Zealand ASD Guideline 2008)[vi]

All children with ANY of the following findings MUST be referred for a general developmental assessment:

- No babble, pointing to or showing of objects or other gesture by 12 months
- No meaningful single words by 18 months
- No two-word spontaneous (non-echoed or imitated) phrases by 24 months
- ANY loss of any language or social skills at ANY age

Key signs in Children aged 1-3 years

Social impairments

- Lack of social smile and lack of eye contact
- Lack of imitation of actions (e.g., clapping)
- Deficits in joint attention, such as lack of showing to share interests or involving others in joint play with toys or other objects
- Lack of interest in other children or odd approaches to other children
- Minimal recognition or responsiveness to another's happiness or distress
- Not wanting to be picked up and cuddled
- Odd relationships with adults (either too friendly or distant)
- Limited variety of imaginative play
- Lack of pretend play, especially involving social imagination (i.e., not joining with others in shared imaginary games)
- Appearing to be "in his/her own world"
- Failure to initiate play with others or participate in early social games
- Preference for solitary play activities

[vi] Reproduced with permission from Ministries of Health and Education. New Zealand Autism Spectrum Disorder Guideline. Wellington: Ministry of Health 2008.

(New Zealand ASD Guideline 2008)

Key signs in Children aged 1-3 years (con't)

Communication impairments

- Impairment in language development, especially comprehension
- Unusual use of language
- Poor response to name
- Deficient non-verbal communication (e.g., lack of pointing and difficulty following the pointing of others)
- Failure to smile socially to share enjoyment and respond to the smiling of others
- Abnormalities in language development, including muteness, odd or inappropriate intonation patterns, persistent echolalia, reference to self as 'you' or 'she/he' beyond three years, unusual vocabulary for child's age/social group
- Limited use of language for communication and/or tendency to talk freely only about specific topics

Impairments of interests, activities and other behaviours

- Over-liking for sameness and/or inability to cope with changes especially in an unstructured setting
- Repetitive play with toys (e.g., lining up objects or turning light switches on and off, regardless of scolding)
- Over-attentiveness to small visual details (e.g., fascination with spinning wheels)
- Repetitive motor mannerisms
- Lack of flexible, cooperative imaginative play or creativity (although certain imaginary scenarios, such as those copied from videos or cartoons may be frequently re-enacted alone)
- Difficulty in organising self in relation to unstructured space (e.g., hugging the perimeter of playgrounds, halls)

(New Zealand ASD Guideline 2008)

Key signs in Children aged 1-3 years (con't)

Other factors which may support a diagnosis of ASD

- Over or under-sensitivity to
  - sound (e.g., has trouble keeping on task with background noise, responds negatively to unexpected /loud noises)
  - touch (e.g., discomfort during grooming, avoids getting messy, picky eater, especially certain textures)
  - movement (e.g., becoming anxious or distressed when feet leave the ground, or twirls/spins/rocks self frequently during the day)
  - visual stimuli (e.g., prefers to be in the dark, feels discomfort or avoids bright lights)
  - smells (e.g., seeks out certain smells)

Key signs in Children aged 4-8 years

Communication impairments

- abnormalities in language development, including muteness, odd or inappropriate intonation patterns, persistent echolalia, reference to self as 'you' or 'she/he' beyond 3 years, unusual vocabulary for child's age /social group
- Limited use of language for communication and/or tendency to talk freely only about specific topics

Social impairments

- Inability to join in with the play of other children, or inappropriate attempts at joint play (may manifest as aggressive or disruptive behaviour)
- Lack of awareness of classroom 'norms' (criticizing teachers, overt unwillingness to cooperate in classroom activities; inability to appreciate/follow current trends, e.g., with regard to other children's dress, style of speech, interests, etc)
- Easily overwhelmed by social and other stimulation
- Failure to relate normally to adults (too intense/no relationship)
- Showing extreme reactions to invasion of personal space and extreme resistance to being 'hurried'

(New Zealand ASD Guideline 2008)

Key signs in Children aged 4-8 years (con't)

Impairment of interests, activities and behaviours

- Lack of flexible, cooperative imaginative play or creativity (although certain imaginary scenarios, such as those copied from videos or cartoons may be frequently re-enacted alone)
- Difficulty in organising self in relation to unstructured space (e.g., hugging the perimeter of playgrounds, halls)
- Inability to cope with change or unstructured situations, even ones that other children enjoy (such as school trips, teachers being away)
- Preoccupation with restricted patterns of interests that are abnormal either in intensity or focus; over-attention to parts of objects

Other factors which may support a diagnosis of ASD

- Unusual profile of skills/deficits (e.g., social and motor skills very poorly developed, whilst general knowledge, reading or vocabulary skills are well above chronological/mental age)
- Any other evidence of odd behaviours, including over or under-sensitivity to sound (e.g., has trouble functioning when there is noise around), touch (e.g., difficulties standing in line or close to others, avoids getting messy, or excessively touches people or objects), movement (e.g., avoids playground equipment or moving toys, or seeks all kind of movement, and this interferes with daily routines), visual stimuli (e.g., prefers to be in the dark, feels discomfort or avoids bright lights), smells (e.g., deliberately smells objects)
- Unusual responses to movement (e.g., toe walking and hand flipping)
- Unusual responses to pain
- Any significant history of loss of skills

Note: these factors in isolation are not indicative of ASD. They are intended to alert professionals to think about the possibility of ASD – whether and when they make referral will depend on the overall situation

Annex C Sources of information and support in Singapore for the family and caregivers

Autism Resource Centre (Singapore)
5, Ang Mo Kio Avenue 10, Singapore 569739
Tel:(65) 6323 3258
Fax: (65) 6323 1974
http://www.autism.org.sg/main/index.php
Email: arc@autism.org.sg

Autism Association (Singapore)
Blk 381, Clementi Avenue 5
#01-398
Singapore 120381
Tel : (65) 6774 6649
Fax : (65) 6774 6957
http://www.autismsg.org/autism/index.html
Email: autism@singnet.com.sg

AWWA Centre for Caregivers
11 Lorong Napiri, Singapore 547532
Tel: (65) 6511 5280
http://www.awwa.org.sg/

The Rainbow Centre Training & Consultancy
Rainbow Center
501 Margaret Drive, Singapore 149306
Tel: (65) 6472 7077
http://www.rainbowcentre.org.sg/

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://smj.sma.org.sg/cme/smj/index.html. The answers will be published in the SMJ May 2010 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Choose True or False.

		True	False
1.	At present, the world wide prevalence of ASD ranges from:		
	A) 20-30 per 10,000 school-aged children	☐	☐
	B) 30-40 per 10,000 school-aged children	☐	☐
	C) 40-50 per 10,000 school-aged children	☐	☐
	D) 50-60 per 10,000 school-aged children	☐	☐
2.	Children with one or more of the following clinical features must be referred promptly for comprehensive developmental evaluation:		
	A) Any loss of language or social skills at any age	☐	☐
	B) No babble, pointing or other gesture by 12 months	☐	☐
	C) No single words by 12 months	☐	☐
	D) No spontaneous (non-echoed) 2-word phrases by 24 months	☐	☐
3.	The following statements are TRUE regarding ASD:		
	A) The etiology of ASD is multifactorial.	☐	☐
	B) Early regression of language skills in ASD children before 3 years of age is associated with poor prognosis.	☐	☐
	C) There is insufficient evidence for a causal relationship between exposure to thimerosal and neuro-developmental disorders.	☐	☐
	D) Active surveillance by primary healthcare professionals at 18 months and again at 24-36 months for warning signs of ASD is recommended.	☐	☐

		True	False
4.	The following statements are TRUE regarding screening for ASD:		
	A) Screening for ASD in the general population is recommended.	☐	☐
	B) No single ASD-specific screening instrument has been identified as ideal for primary screening of a general population of children.	☐	☐
	C) Screening for ASD in a high-risk population is not recommended.	☐	☐
	D) Current evidence suggests that the CHecklist for Autism in Toddlers (CHAT) at 18 months and Modified CHecklist for Autism in Toddlers (M-CHAT) at 18-24 months are useful for primary screening of ASD.	☐	☐
5.	Which of the following conditions is/are associated with ASD:		
	A) Fragile X syndrome	☐	☐
	B) Down syndrome	☐	☐
	C) Prader Wili syndrome	☐	☐
	D) Tuberous sclerosis	☐	☐
6.	Which of the following statement is FALSE regarding investigations for ASD?		
	A) Serum lead screening is routinely indicated in children with ASD.	☐	☐
	B) Immunologic investigation is not routinely indicated in children with ASD.	☐	☐
	C) Brain imaging is routinely recommended in children with ASD.	☐	☐
	D) Investigations to identify yeast over-growth in the gastro-intestinal tract are not recommended in children with ASD.	☐	☐

		True	False
7.	The following statement is/are TRUE regarding Methylphenidate:		
	A) In Singapore, methylphenidate is the most commonly used stimulant medication for attention deficit hyperactivity disorder.	☐	☐
	B) It is a potent peripheral nervous system stimulant derived from amphetamine.	☐	☐
	C) It is thought to exert its effect by enhancing dopaminergic transmission in the brain.	☐	☐
	D) Methylphenidate may be considered for treating hyperactivity in children with ASD.	☐	☐
8.	Typical antipsychotics such as Haloperidol is associated with the following significant side effects:		
	A) Excessive weight gain	☐	☐
	B) Excessive sedation	☐	☐
	C) Acute dystonic reactions	☐	☐
	D) Decreased irritability	☐	☐
9.	Which of the following complementary alternative therapies are NOT recommended for pre-school children with ASD because of insufficient, conflicting or inconclusive evidence:		
	A) Amino acid supplementation	☐	☐
	B) Expressive psychotherapy	☐	☐
	C) Hyperbaric Oxygen Therapy	☐	☐
	D) Omega-3 fatty acid (O3FA) supplementation	☐	☐
10.	The following complementary alternative therapies are NOT recommended in pre-school children with ASD because of potential for harm or adverse effects		
	A) Chelation therapy	☐	☐
	B) Facilitated Communication	☐	☐
	C) Music therapy	☐	☐
	D) Auditory Integration Therapy	☐	☐

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DISCLAIMER

In as much as the guideline serves to provide direction to medical and non-medical professional rendering care and service to pre-school children with ASD, it is not a textbook or protocol for all children with autism. Care for the particular child must be individualised and based on the best available information based on the child's strengths and weaknesses.

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