3-year scoping report

Topic: Assessment, diagnosis and interventions for autism spectrum disorders SIGN 145

Date of search: March 2019 (conducted by Juliet Brown, Evidence and Information Scientist)
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Background

The purpose of this scoping is to identify recent secondary evidence that may be relevant to guideline (SIGN 145) on the assessment, diagnosis and interventions for autism spectrum disorders.

A rapid high-level search of the literature was conducted using a predefined list of resources. The search focused on secondary sources of evidence (health technology assessments, evidence-based guidelines, systematic reviews and meta-analyses) and was limited to evidence published, in English language, since 2014. The results have been mapped to the relevant section of the guideline, then assessed on whether the results are likely to significantly change the content of SIGN 145 (see section 2). The results of the evidence review are based mainly on information contained within the executive summaries or abstracts of the evidence identified. A comprehensive assessment and critical analysis of the evidence was not carried out.

The scoping report and proposed areas for update were circulated to the original guideline group for comment. The feedback is in section 3. The priority rating in section 1 is based on this feedback.

Decision

The Guideline Programme Advisory Group considered the evidence and the feedback at a meeting on 29 May 2019. The group concluded that no evidence had been identified that would significantly change the key recommendations. The guideline is revalidated and will be considered for update again in 2023.

Section 1: Proposed areas for update/areas where new evidence has been identified and could be considered for update

Section	Details of update	KQ	Priority
4.1.3	There are a number of new studies of identification tools which could be reviewed to see if one can be recommended over the other? NB NICE didn't update, and evidence doesn't seem to be conclusive about which to use.	2	Low
4.1.6 Identifying adults for assessment	New systematic reviews could add to the evidence on gender dysphoria. There is now a systematic review on suicidality.	17	Desirable
4.6 Prognostic indicators	Two new systematic reviews which could be considered for inclusion.	1a	Desirable
6.3.5 Sensory integration therapy	There are new systematic reviews which may provide more evidence.	11	Desirable
6.3.6 Music therapy	A new large RCT on music therapy would change wording of recommendation.		Not required
6.4 Nutritional interventions	New systematic review which concludes omega-3 fatty acid shows no difference.	13	Desirable
6.5 Other interventions	New systematic reviews on exercise interventions, parent training for disruptive behaviour.		Desirable
8.2 Antipsychotics	Updated Cochrane review includes one new trial which provides evidence on risk of relapse after discontinuation of aripiprazole.	14	Desirable
8.4 Noradrenergic reuptake indicators	New meta-analysis shows benefit.	14	Desirable
8.7.2/9.10.2 Oxytocin	New studies could provide further evidence. Only small pilot studies cited at present.	14, 21	Not required
8.8 Melatonin for children and young people	Melatonin RCT could be added to support the evidence (3-month data), however it is unlikely to change the recommendation.	12	Not required
Annex 3	New systematic reviews on increased risk due to hypertensive disorders during pregnancy or infection during pregnancy.	1	Desirable

Section 2: Results of the scoping search

Overarching guidelines			Impact on guideline
	Howes (2018) Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology, Journal of Psychopharmacology 2018;32(1):3-29	Draws on NICE 2012 for non-pharmacological sections but may be helpful for pharmacological references. Updated references on oxytocin compared with SIGN 145 note consensus is 'further studies are required to fully investigate oxytocin before it can be recommended for routine use'. Highlights recent studies on Glutamatergic agents. GABA agonists eg arbaclofen – not in SIGN 145 'insufficient evidence to recommend'.	Does not provide new evidence. No action required.
	NICE. Autism spectrum disorder in under 19s: recognition, referral and diagnosis (NICE guideline CG128). Surveillance report 2016	New evidence was identified for: • babies small for gestational age. • prenatal use of selective serotonin reuptake inhibitors (SSRIs). • fertility treatments. On review, the evidence did not result in changes to the guideline. Moderate-quality evidence from three cross-sectional studies containing 1,914,808 children (9 years and younger) found that more children with ADHD had a diagnosis of ASD compared to children without ADHD. The guideline was updated in December 2017 to add attention deficit hyperactivity disorder to the list of factors associated with an increased prevalence of autism.	The association between ASD and ADHD is already highlighted in sections 4.1.6 and 4.4 of SIGN 145. No action required.

	NICE. Autism spectrum disorder in under 19s: support and management (NICE guideline CG170). Surveillance report 2016	51 new studies were identified through surveillance of this guideline. This included new evidence that supports current recommendations on: • general principles of care (access to health and social care services, knowledge and competence of health and social care professionals, information and involvement in decision making) • families and carers • specific interventions for the core features of autism • interventions for behaviour that challenges • interventions for life skills • interventions aimed at improving the impact on the family • interventions for autism that should not be used • interventions for coexisting problems • transition to adult services. There was no new evidence on: • general principles of care (organisation and delivery of services, making adjustments to the social and physical environment and processes of care). None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.	No action required.

	NICE. Surveillance report 2016 – Autism spectrum disorder in adults (2012) NICE guideline CG142 https://www.nice.org.uk/guidance/cg142/resources/surveillance-report-2016-autism-spectrum-disorder-in-adults-2012-nice-guideline-cg142-2600145325/chapter/Surveillance-decision?tab=evidence#reason-for-the-decision	NICE found 50 new studies through surveillance of this guideline. This included new evidence on: • assessment, monitoring and management of coexisting conditions in adults with autism • identifying the correct interventions and monitoring their use • the effectiveness of vocational and supported employment programmes • psychosocial interventions • biomedical interventions, including complementary and alternative medicine and physiotherapy • organisation and delivery of care. No new evidence was found on: • experiences of families, partners and carers of adults with autism • signs and symptoms of possible autism • methods/tools for case identification • the effectiveness of educational interventions • factors that moderate the effectiveness of interventions • the role of families, partners and carers in supporting the delivery of interventions • information and day-to-day support for families, partners and carers • essential elements in the effective provision of support services for the individual, day care and residential care None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.	No action required.

	Section 3 Diagnostic criteria		
	NIL		No action required.
	Section 4 Recognition, assessment, diagnosis		
4	HAS (French) 2018 Autism spectrum disorder: Warning signs, detection, diagnosis and assessment in children and adolescents. Best practice guideline in English (https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-04/cpg_asd_diagnostic_assessment_child_teenager_2018.pdf)	Evidence review only in French language. It appears there are not too many very recent references. Likely this French update quite specific to organisational context. Has recommendations on 'announcing the diagnosis'. (links to SIGN section 11)	Does not provide new evidence. No action required.
4.1.3	Fusaroli (2017) Is voice a marker for Autism spectrum disorder? A systematic review and meta-analysis. Autism research : Official Journal of the International Society for Autism Research 2017;10(3):384-407	The methods used and the acoustic features investigated were too diverse for performing meta-analysis. We conclude that multivariate studies of acoustic patterns are a promising but yet unsystematic avenue for establishing ASD markers.	The evidence is not sufficiently conclusive to include in the guideline. No action required.
4.1.4 /4.1.7	Hirota (2018) A systematic review of screening tools in non-young children and adults for autism spectrum disorder. Research in Developmental Disabilities 2018;80(1-12)	Search to March 2017. 14 studies (11 children, 3 adults). Only three screening tools (the Autism-Spectrum Quotient, the Social Communication Questionnaire, and the Social Responsiveness Scale) were examined in more than two studies. These tools may assist in differentiating ASD from other neurodevelopmental and psychiatric disorders or typically developed children. In young adult	This evidence would not change the current recommendations. No action required.

	https://www.sciencedirect.com/science/article/pii/S0891422218301306?via%3Dihub#sec0075	populations, the paucity of the existing research in this group limits definitive conclusion and recommendations.	
4.2.3	Randall (2018) Diagnostic tests for autism spectrum disorder (ASD) in preschool children Cochrane Database of Systematic Reviews https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009044.pub2/epdf/full	Review up to date as of July 2016. Current findings suggest that ADOS is best for not missing children who have ASD and is similar to CARS and ADI-R in not falsely diagnosing ASD in a child who does not have ASD. ADOS has acceptable accuracy in populations with a high prevalence of ASD. However, overdiagnosis is likely if the tool is used in populations with a lower prevalence of ASD. This finding supports current recommended practice for ASD diagnostic tools to be used as part of a multi-disciplinary assessment, rather than as stand-alone diagnostic instruments.	Does not change the current advice. No action required.
4	Australian Government, Autism CRC (2018) A National Guideline for the Assessment and Diagnosis of Autism Spectrum Disorders in Australia	Guidelines to promote consistency in processes for diagnoses. Combined published evidence (including SIGN 145) (acknowledged paucity of high-quality evidence) with expert consensus and information from a range of community and patient consultation methods. Reached 70 graded recommendations – specific to their national clinical context. May be some points of interest to SIGN eg co-ordination of diagnosis, use of telehealth, single practitioner evaluation, sharing findings, cultural and linguistic diversity, remote locations, consideration of trauma/attachment issues.	Insufficient evidence base to support an update of the guideline. No action required.
4.1.3	Yuen (2018) Assessing the accuracy of the Modified Checklist for Autism in Toddlers: a systematic review and	Search to May 2016 The Modified Checklist for Autism in Toddlers (M-CHAT) performs with low-to-moderate accuracy in children with developmental concerns. There is limited	Evidence does not change what is already covered in the guideline. No action required.

	meta-analysis. Developmental Medicine & Child Neurology 2018;60(11):1093-1100	evidence supporting its use at 18 months or in low-risk children.	
4.1.6	Zahid (2017) Suicidality in Autistic Spectrum Disorders. Crisis: Journal of Crisis Intervention & Suicide 2017;38(4):237-246 https://econtent.hogrefe.com/doi/full/10.1027/0227-5910/a000458?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&	A systematic review including 12 papers with a total sample size of 2,651. Suicidal attempts and ideation are increased in people with ASD; however, the extent of the increase and the risk factors identified within this group remain underinvestigated. Prevalence of suicide attempts varied between 7% and 47%, while suicidal ideation was reported in up to 72% of cases. Papers were cross sectional and contained a number of limitations. Only one paper used the gold standard for diagnosis of ASD and one a standardised measure of suicidal behaviour. There is a lack of research on protective factors. The correlation between ASD and suicidality needs further examination with longitudinal research. Not presently within SIGN guideline.	Could be added, although evidence is weak.
4.1.6	Van Der Miesen (2016) Gender dysphoria and autism spectrum disorder: A narrative review. International Review of Psychiatry 2016;28(1):70-80	Systematic search. 25 articles. GD and ASD were found to co-occur frequently - sometimes characterised by atypical presentation of GD.	Could be added to section 4.1.6. Gender dysphoria is already highlighted, with reference to one study.
4.1.6	Glidden (2016) Gender Dysphoria and Autism Spectrum Disorder: A Systematic Review of the Literature. Sexual Medicine Reviews 2016;4(1):3-14	Search to July 2015 identified 19 articles. Although the research is limited, especially for adults, there is an increasing amount of evidence that suggests a co-occurrence between gender dysphoria and ASD.	Could be added to section 4.1.6. Gender dysphoria is already highlighted, with reference to one study.
4.1.7	Chesnut (2017)	This study systematically examined the accuracy of the Social Communication Questionnaire as a function	This is already covered in Annex 4. No action required.

	A meta-analysis of the social communication questionnaire: Screening for autism spectrum disorder. Autism 2017;21(8):920-928 https://journals.sagepub.com/doi/full/10.1177/1362361316660065?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed	of the methodological decisions made by researchers screening for autism spectrum disorder over the last 15 years. Findings from this study suggest that the Social Communication Questionnaire is an acceptable screening instrument for autism spectrum disorder (area under the curve = 0.885).	
4.1.7	Baghdadli (2017) Measurement properties of screening and diagnostic tools for autism spectrum adults of mean normal intelligence: A systematic review. European Psychiatry: the Journal of the Association of European Psychiatrists 2017;44(104-124)	Among screening tools, only AQ-50, AQ-S, and RAADS-R and RAADS-14 were found to provide satisfactory or intermediate values for their psychometric properties, supported by strong or moderate evidence. Nevertheless, risks of bias and concerns on the applicability of these tools limit the evidence on their diagnostic properties. We found that none of the gold standard diagnostic tools used for children had satisfactory measurement properties. There is limited evidence for the measurement properties of the screening and diagnostic tools used for AS adults with a mean normal range of measured intelligence.	This does not add anything new to what is already included in SIGN 145.
4.1.8	Loomes (2017) What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. Journal of the American Academy of Child & Adolescent	Meta-analysis of prevalence studies conducted since the introduction of the DSM-IV and the ICD-10. 54 studies. Of children meeting criteria for ASD, the true male-to-female ratio is not 4:1, as is often assumed; rather, it is closer to 3:1. There appears to be a diagnostic gender bias, meaning that girls who meet criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis.	This issue is already highlighted in the guideline. The new evidence is unlikely to change the existing recommendation. No action required.

	Psychiatry 2017;56(6):466-474 https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0890856717301521?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0890856717301521%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2Fpubmed%2F28545751		
4.2.2	Galliver (2017) Cost of assessing a child for possible autism spectrum disorder? An observational study of current practice in child development centres in the UK.	Limited but UK cost study. Costs based on professional time input. 12/20 centres responded.	The results would not significantly impact on the guideline. They may be of interest for discussions on implementation.
4.3.1	Broome (2017) A Systematic Review of Speech Assessments for Children With Autism Spectrum Disorder: Recommendations for Best Practice. American Journal of Speech-Language Pathology 2017;26(3):1011-1029	Systematic review to 2014. 21 articles. Clinical and research guidelines for speech assessment of children with ASD are outlined. The participants, assessment tasks and reporting standards in the studies included in the systematic review varied widely. Although a number of well-designed studies with clear diagnostic criteria have been completed, without standard reporting protocols for speech sampling and analysis, it remains difficult to draw comparisons between studies. Given this heterogeneity, the results do not provide clear clinical or research guidelines for best practice in the speech assessment of children with ASD.	No action required.

4.5	AIM Clinical Appropriateness Guidelines for Genetic Testing for Single-Gene and Multifactorial Conditions	Cites the American College of Medical Genetics (ACMG) recommendation that chromosomal microarray as a first-tier test in the initial postnatal evaluation of individuals with multiple anomalies not specific to a well-delineated genetic syndrome, apparently non-syndromic developmental delay/intellectual disability, and autism spectrum disorders.	Does not change what is already stated. No action required.
4.5	Rinaldi (2017) Guideline recommendations for diagnosis and clinical management of Ring14 syndrome-first report of an ad hoc task force. Orphanet Journal Of Rare Diseases 2017;12(1):69	US guidelines. Ring chromosome 14 syndrome is a rare chromosomal disorder characterised by early onset refractory epilepsy, intellectual disability, autism spectrum disorder and a number of diverse health issues. Conventional cytogenetics is the primary tool to identify a ring chromosome. Children with a terminal deletion of chromosome 14q ascertained by molecular karyotyping (CGH/SNP array) should be tested secondarily by conventional cytogenetics for the presence of a ring chromosome. Likely rare – but may add to section 4.5	This is already covered by the good practice point to seek advice on further testing from local genetics services. No action required.

4.6?	Bieleninik (2017) Tracing the temporal stability of autism spectrum diagnosis and severity as measured by the Autism Diagnostic Observation Schedule: A systematic review and meta-analysis. PLoS ONE [Electronic Resource] 2017;12(9):e0183160 https://journals.plos.org/plosone/article/related?id=10.1371/journal.pone.0183160	40 studies to October 2015. Analyses showed no change in ADOS scores across time as measured by Calibrated Severity Scores (mean difference [MD] = 0.05, 95% CI -0.26 to 0.36). A minor but statistically significant change in ADOS total raw scores was observed (MD = -1.51, 95% CI -2.70 to -0.32). There was no improvement in restricted and repetitive behaviours (standardised MD [SMD] = -0.04, 95% CI -0.19 to 0.11), but a minor improvement in social affect over time (SMD = -0.31, 95% CI -0.50 to -0.12). No changes were observed for meeting the autism spectrum disorder criteria over time (risk difference [RD] = -0.01, 95% CI -0.03 to 0.01), but a significant change for meeting autism criteria over time (RD = -0.18, 95% CI -0.29 to -0.07). On average, there was a high heterogeneity between studies (I^2 range: 65.3% to 93.1%). Overall autism core symptoms were remarkably stable over time across childhood indicating that intervention studies should focus on other areas, such as quality of life and adaptive functioning.	This could be added to section 4.6
4.6	Steinhausen (2016) A systematic review and meta-analysis of the long-term overall outcome of autism spectrum disorders in adolescence and adulthood. Acta Psychiatrica Scandinavica 2016;133(6):445-52	Search to Aug 2015. 15 studies. Total of 828 individuals with autistic disorders were included in the analyses. An estimated 19.7% (95%CI: 14.2 to 26.6) had a good outcome, 31.1% (95%CI: 23.2 to 40.4%) a fair outcome, and 47.7% (95%CI: 36.6 to 59.0) a poor outcome (global measure of adjustment).	This could be added to section 4.6
	Section 6 Non-pharmacological interventions – children and young people		
6	Tachibana (2017) A systematic review and meta-analysis of comprehensive	Compared behavioural, social-communication focused, and multimodal developmental interventions. 32 RCTs – 14 synthesised.	Evidence is inconclusive. No action required.

	interventions for pre-school children with autism spectrum disorder (ASD). PLoS ONE 2017;12(12):e0186502	The small number of studies included in the present study limited the ability to make inferences when comparing the three models and investigating the strengths and weaknesses of each type of intervention with respect to important outcomes.	
6.2	Brignell (2018) Communication interventions for autism spectrum disorder in minimally verbal children Cochrane Database of Systematic Reviews	Review to Nov 2017. Only two studies met inclusion criteria, one on focused playtime intervention and one on PECS. Both had communication outcomes. There is currently limited evidence that verbally-based and ACC interventions improve expressive communication skills in minimally verbal children with ASD aged 32 months to 11 years. Additional trials that use communication interventions and compare the effects of these interventions to a control group are urgently required to build the evidence base.	This evidence does not change the existing recommendation. No action required.
6.2	Parsons (2017) A systematic review of pragmatic language interventions for children with autism spectrum disorder. PLoS ONE 2017;12(4):e0172242	Search to May 2016 identified 22 studies reporting on 20 pragmatic language interventions for children with ASD aged 0-18 years. A majority of the interventions reviewed (14 out of 20) targeted non-verbal communication, a hallmark impairment of ASD. Findings of this meta-analysis suggest that the person(s) of focus is a significant mediator of intervention effect, but the age of participants is not, suggesting that regardless of age, the child with ASD and their parent must be actively included in an intervention in order to maximise benefits. Further, group interventions appear to be more effective than those delivered one-on-one, and the inclusion of typically developing peers may have the potential to increase the effectiveness of group interventions.	This evidence does not change the existing recommendation. No action required.
6.2.1	Murza (2016) Joint attention interventions for children with autism spectrum disorder: a systematic	Fifteen randomised experimental studies. All comparisons resulted in statistically significant effects, although overlapping confidence intervals suggest that none of the comparisons were statistically different from each other. Specifically, treatment	This evidence does not change the existing recommendation. No action required.

	review and meta-analysis. International Journal of Language & Communication Disorders 2016;51(3):236-51	administrator, dosage and design (control or comparison, etc.) characteristics of the studies do not appear to produce significantly different effects. The results of this meta-analysis provide strong support for explicit joint attention interventions for young children with ASD; however, it remains unclear which children with ASD respond to which type of intervention.	
6.2.1	Hampton (2016) Intervention effects on spoken-language outcomes for children with autism: a systematic review and meta-analysis. Journal of Intellectual Disability Research 2016;60(5):444-63	Meta-analysis of 26 studies of spoken-language outcomes for children with ASD who received early intervention as compared with usual treatments. Early intervention improves spoken-language outcomes for children with ASD, and the largest effects are found when both parent and clinician implement the intervention.	This evidence does not change the existing recommendation. No action required.
6.2.2	Pennisi (2016) Autism and social robotics: A systematic review. Autism research : Official Journal of the International Society for Autism Research 2016;9(2):165-83	Robots provide therapists and researchers a means to connect with autistic subjects in an easier way, but studies in this area are still insufficient	This is not robust enough for inclusion. No action required.
6.2.2	Gates (2017) Efficacy of group social skills interventions for youth with autism spectrum disorder: A systematic review and meta-analysis. Clinical Psychology Review 2017;52(164-181)	19 studies to Jan 2016. May update SIGN 145 refs 145/6. Results show that overall positive aggregate effects were medium ($g=0.51$, $p< 0.001$). Social skills interventions presently appear modestly effective for youths with ASD, but may not generalise to school settings or self-reported social behavior. See also: • Jonsson (2016) Can findings from randomised controlled trials of social skills training in	This evidence draws similar conclusions to the evidence already stated in the guideline. No action required.

	https://www.sciencedirect.com/science/article/pii/S0272735816303520?via%3Dihub	autism spectrum disorder be generalised? The neglected dimension of external validity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5996019/ (not in search)	
6.2.2	Tachibana (2018) Meta-analyses of individual versus group interventions for pre-school children with autism spectrum disorder (ASD). PLoS ONE 2018;13(5):e0196272	14 trials included. Results suggested that both individual and group interventions showed significant effects compared to the control condition on 'reciprocity of social interaction towards others' (SMD 0.59 95% CI 0.25 to 0.93; 0.45 95% CI 0.02 to 0.88 respectively). No significant difference on all the outcomes between the individual and group interventions. Targets for interventions may include 'reciprocity of social interaction towards others' and 'parental sychrony'.	This would enhance the evidence base but not change the recommendation. No action required.
6.3	Lydon (2017) A systematic review and evaluation of inhibitory stimulus control procedures as a treatment for stereotyped behavior among individuals with autism. Developmental neurorehabilitation 2017;20(8):491-501	Inhibitory stimulus control procedures (ISCPs) comprise a type of antecedent-based intervention that has been proposed as an effective treatment approach for stereotypy. 11 studies. ISCPs comprise a promising intervention for stereotyped behaviour but further research is required	Results inconclusive. No action required.
6.3.1	Reichow (2018) Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews 2018;5 https://www.cochranelibrary.com/cdsr/doi/10.1002/14	Cochrane review – update of SIGN guideline reference 159. New search is to August 2017. Included five studies (one RCT and four CCTs) with a total of 219 children. Low quality-evidence at post-treatment that EIBI improves adaptive behaviour and reduces autism symptom severity compared to treatment as usual. No adverse effects were reported across studies. Low-quality evidence at post-treatment that EIBI improves	Previous Cochrane review concluded EIBI could be considered on a case-by-case basis. This review concludes that EIBI providers should be aware of the current evidence and use clinical decision-making guidelines, such as seeking the family's input and drawing upon prior clinical experience, when making recommendations to clients on the use EIBI.

	651858.CD009260.pub3/full	IQ, expressive and receptive language skills and problem behaviour compared with treatment as usual.	This does not change the recommendation in the guideline. No action required.
6.3.1	Caron (2017) Implementation evaluation of early intensive behavioral intervention programs for children with autism spectrum disorders: A systematic review of studies in the last decade. Evaluation & Program Planning 2017;62(1-8)	Purpose of the study was to 1) review the studies having evaluated the EIBIs provided to children with ASD over the past ten years(to 2015), 2) examine which implementation components were documented, and 3) check whether this information was linked to the data on the effects. Essentially a review of methodology. Unlikely to add to section.	No action required.
6.3.2	Spain (2017) Family therapy for autism spectrum disorders Cochrane Database of Systematic Reviews http://dx.doi.org/10.1002/14651858.CD011894.pub2	Search to Jan 2017. No high quality RCTs identified. No studies have compared family therapy with either no treatment, a group of people waiting to start treatment, or another type of psychological therapy. There is one study awaiting classification.	No evidence found. No action required.
6.3.2	Wright (2016) Social Stories to alleviate challenging behaviour and social difficulties exhibited by children with autism spectrum disorder in mainstream schools: design of a manualised training toolkit and feasibility study for a cluster randomised controlled trial with nested qualitative and cost-effectiveness components.	NIHR HTA (including systematic review) which links to research recommendation in SIGN 145. The review found that the research into social stories is predominantly based in the USA, carried out in under-12-year-olds and using single-case designs. Most studies either did not follow established Social Story criteria or did not report if they did. The assessment of effectiveness presents a largely positive picture but is limited by methodological issues.	Did not identify anything new to add to the guideline.

	Health Technology Assessment: 2016 https://www.journalslibrary.nihr.ac.uk/hta/hta20060#/abstract		
6.3.5	Weitlauf (2017) Interventions Targeting Sensory Challenges in Autism Spectrum Disorder: A Systematic Review. Pediatrics 2017;139(6)	24 studies were small and short-term, and few fully categorised populations. Some interventions may yield modest short-term (<6 months) improvements in sensory- and ASD symptom severity-related outcomes; the evidence base is small, and the durability of the effects is unclear. Although some therapies may hold promise, substantial needs exist for continuing improvements in methodological rigor. In agreement with recommendations for research.	This evidence is insufficient to impact on the guideline. No action required.
6.3.5	Schaaf (2018) Efficacy of Occupational Therapy Using Ayres Sensory Integration: A Systematic Review. American Journal of Occupational Therapy 2018;72(1) https://ajot.aota.org/article.aspx?articleid=2666688	Three RCTs to 2015. The evidence is strong that ASI intervention demonstrates positive outcomes for improving individually generated goals of functioning and participation as measured by Goal Attainment Scaling for children with autism. Moderate evidence supported improvements in impairment-level outcomes of improvement in autistic behaviours and skills-based outcomes of reduction in caregiver assistance with self-care activities. Links to research recommendation in SIGN 145 See also • Pfeiffer (2018) Effectiveness of Cognitive and Occupation-Based Interventions for Children With Challenges in Sensory Processing and Integration: A Systematic Review https://ajot.aota.org/article.aspx?articleid=2665225	The evidence from these systematic reviews could provide further evidence on sensory integration. This section currently only supports a good practice point: "Children and young people affected by ASD may benefit from occupational therapy, advice and support in adapting environments, activities and routines in daily life." Consider for update.

		• Feldman (2018) Audiovisual multisensory integration in individuals with autism spectrum disorder: A systematic review and meta-analysis https://www.sciencedirect.com/science/article/pii/S0149763418303634?via%3Dihub • Bodison (2018) Specific Sensory Techniques and Sensory Environmental Modifications for Children and Youth With Sensory Integration Difficulties: A Systematic Review https://ajot.aota.org/article.aspx?articleid=2666720	
6.3.6	Crawford (2017) International multicentre randomised controlled trial of improvisational music therapy for children with autism spectrum disorder: TIME-A study. Health Technology Assessment: 2017 Also published at : BieleninikL, GeretseggerM, MösslerK, AssmusJ, ThompsonG, and GattinoGet al. Effects of improvisational music therapy versus enhanced standard care on symptom severity among children with autism spectrum disorder: the TIME-A randomized clinical trial.	NIHR HTA 364 participants were randomised between 2011 and 2015. A total of 182 children were allocated to IMT (90 to high-frequency sessions and 92 to low-frequency sessions), and 182 were allocated to enhanced standard care alone. A total of 314 (86.3%) of the total sample were followed up at five months [165 (90.7%) in the intervention group and 149 (81.9%) in the control group]. Among those randomised to IMT, 171 (94.0%) received it. From baseline to five months, mean scores of ADOS social affect decreased from 14.1 to 13.3 in music therapy and from 13.5 to 12.4 in standard care [mean difference: music therapy *v*. standard care = 0.06, 95% confidence interval (CI) -0.70 to 0.81], with no significant difference in improvement. There were also no differences in the parent-rated social responsiveness score, which decreased from 96.0 to 89.2 in the music therapy group and from 96.1 to 93.3 in the standard care group over this period (mean difference: music therapy *v*. standard care = -3.32, 95% CI –7.56 to 0.91). Adding IMT to the treatment received by	This RCT would update the evidence statement, but would not lead to a recommendation.

	JAMA2017; 318: 523- 4. https://doi.org/10.1001/jama.2017.9478	children with ASD did not improve social affect or parent-assessed social responsiveness. Large RCT – may change conclusion of Cochrane Review 9SIGN ref 171) https://www.journalslibrary.nihr.ac.uk/hta/hta21590/#/abstract	
6.3.7 /8.8	Cuomo (2017) Effectiveness of Sleep-Based Interventions for Children with Autism Spectrum Disorder: A Meta-Synthesis. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 2017;37(5):555-578	Meta-synthesis of eight previous reviews. 38 studies overall of 17 sleep domains. Interventions; melatonin therapy, pharmacologic treatments other than melatonin, behavioural interventions, parent education/education programs, and alternative therapies (massage therapy, aromatherapy, and multivitamin and iron supplementation), Melatonin, behavioural interventions, and parent education/education program interventions appear the most effective at ameliorating multiple domains of sleep problems. The results of this meta-synthesis suggest that no single intervention is effective across all sleep problems in children with ASD. See also RCT: • Maras (2018) Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder https://www.liebertpub.com/doi/full/10.1089/cap.2018.0020 Links to research recommendation in SIGN 145	Meta-synthesis is very broad and likely to cover trials already cited. RCT could be added to support the evidence in 8.8 (3-month data), however it is unlikely to change the recommendation.
6.3.7	McLay (2016) Empirical research evaluating non-traditional approaches to managing sleep problems in children with autism. Developmental	Eight studies on efficacy of non-behavioural and non-pharmacological approaches to the treatment of sleep disturbance in individuals with autism spectrum disorder. Positive outcomes were reported for the use of massage therapy and vitamin supplements. Aromatherapy was reported to have no effect on sleep. The limited body of evidence and the	No change to what is already stated.

	neurorehabilitation 2016;19(2):123-34	methodological limitations suggests that the efficacy of non-traditional approaches to treatment of sleep problems in individuals with autism is yet to be demonstrated.	
6.4	Piwowarczyk (2018) Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review. European Journal of Nutrition 2018;57(2):433-440 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5242335/	Search to Aug 2016, six RCTs 214 participants With few exceptions, there were no statistically significant differences in autism spectrum disorder core symptoms between groups, as measured by standardised scales. See also RCT published since: https://link.springer.com/article/10.1007%2Fs12519-016-0040-z	Guideline states further studies are needed to confirm results. Newer systematic review concludes the same. The RCT concludes that GFD may be effective in controlling gastrointestinal symptoms and ASD behaviours. However, it is a poor-quality study. No action required.
6.4	Sathe (2017) Nutritional and Dietary Interventions for Autism Spectrum Disorder: A Systematic Review. Pediatrics 2017;139(6)	19 RCTs. Studies were small and short term, and there were few fully categorised populations or concomitant interventions. There is little evidence to support the use of nutritional supplements or dietary therapies for children with ASD.	Concurs with what is stated in the guideline. No action required.
6.4	Gogou (2017) The effect of dietary supplements on clinical aspects of autism spectrum disorder: A systematic review of the literature. Brain & Development 2017;39(8):656-664	N-acetylcysteine was shown to exert a beneficial effect on symptoms of irritability. Data on the efficacy of d-cycloserine and pyridoxine-magnesium supplements was controversial. No significant effect was identified for fatty acids, N,N-dimethylglycine and inositol. Literature data about ascorbic acid and methyl B12 were few.	Does not impact on the guideline. No action required.
6.4	Horvath (2017) Omega-3 Fatty Acid Supplementation Does Not Affect Autism Spectrum	Five RCTs (183 participants) up to Aug 2016 were included. With four exceptions, there were no statistically significant differences in ASD symptoms between groups measured by validated scales.	Guideline currently states insufficient evidence on omega-3 fatty acids. Consider inclusion of more recent systematic review.

	Disorder in Children: A Systematic Review and Meta-Analysis. Journal of Nutrition 2017;147(3):367-376 https://academic.oup.com/jn/article/147/3/367/4584808	The limited data currently available suggest that omega-3 fatty acid supplementation does not enhance the performance of children with ASD. See also RCT: • Mazahery (2018) A randomised controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of irritability and hyperactivity among children with autism spectrum disorder https://www.sciencedirect.com/science/article/abs/pii/S0960076018303923 (111 children, secondary reporting on a trial of Vit D) • Keim (2018) omega-3 and omega-6 Fatty Acid Supplementation May Reduce Autism Symptoms Based on Parent Report in Preterm Toddlers https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6251698/ (pilot study of 31 toddlers. Showed improvement.) • Adams (2018) Comprehensive Nutritional and Dietary Intervention for Autism Spectrum Disorder-A Randomized, Controlled 12-Month Trial https://www.mdpi.com/2072-6643/10/3/369 (117 participants, all ages. The treatment group had significantly greater increases in EPA, DHA, carnitine, and vitamins A, B2, B5, B6, B12, folic acid, and Coenzyme Q10. Authors conclude that the positive results of this study suggest that a comprehensive nutritional and dietary intervention is effective at improving nutritional status, non-verbal IQ, autism symptoms, and other symptoms in most individuals with ASD. Participants were not blinded to their treatment, and the randomisation method was at risk of bias.)	

		• Sheppard (2017) Effect of Omega-3 and -6 Supplementation on Language in Preterm Toddlers Exhibiting Autism Spectrum Disorder Symptoms https://link.springer.com/article/10.1007%2Fs10803-017-3249-3 (same study as Keim 2017)	
6.5	Bremer (2016) A systematic review of the behavioural outcomes following exercise interventions for children and youth with autism spectrum disorder. Autism 2016;20(8):899-915 https://journals.sagepub.com/doi/full/10.1177/1362361315616002?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed	13 studies. Results demonstrated that exercise interventions consisting individually of jogging, horseback riding, martial arts, swimming or yoga/dance can result in improvements to numerous behavioural outcomes including stereotypic behaviours, social-emotional functioning, cognition and attention. Horseback riding and martial arts interventions may produce the greatest results with moderate to large effect sizes, respectively. Links to research recommendation in SIGN 145	Consider for update.
6.5	Tan (2016) A Meta-Analytic Review of the Efficacy of Physical Exercise Interventions on Cognition in Individuals with Autism Spectrum Disorder and ADHD. Journal of Autism & Developmental Disorders 2016;46(9):3126-43	The results revealed an overall small to medium effect of exercise on cognition, supporting the efficacy of exercise interventions in enhancing certain aspects of cognitive performance in individuals with ASD and/or ADHD. Links to research recommendation in SIGN 145	Consider for update.

	https://link.springer.com/article/10.1007%2Fs10803-016-2854-x		
	Section 7 Non-pharmacological interventions - adults		
7.1/ 6.2.1	Holyfield (2017) Systematic review of AAC intervention research for adolescents and adults with autism spectrum disorder. Aac: Augmentative & Alternative Communication 2017;33(4):201-212 https://www.tandfonline.com/doi/full/10.1080/07434618.2017.1370495	18 studies to Feb 2017 The main finding of the current systematic review was that augmentative and alternative communication (AAC) intervention appears to be highly effective for adolescents and adults with autism spectrum disorder. However, the limited number of adolescents and adults with ASD who have participated in AAC intervention research to date tempers these findings; the small number of individuals who have participated in this research was a surprising finding of this review. In addition, the inconclusive nature of some studies due to fatal methodological flaws further limited the observations from which effects could be calculated. This resulted in an even smaller number of participants and studies from which the overall finding was drawn.	Evidence is not robust enough to support a recommendation. No action required.
	Section 8 Pharmacological interventions – children and young people		
8.2	Hirsch (2016) Aripiprazole for autism spectrum disorders (ASD) Cochrane Database of Systematic Reviews	Updates ref 195 in SIGN 145 (Ching 2012). Update search October 2015 Conclusions not changed but updated with a new study that evaluates risk of relapse after discontinuation of aripiprazole once symptoms have improved during treatment. http://dx.doi.org/10.1002/14651858.CD009043.pub3	Consider for update.
8.2	Fallah (2019) Atypical Antipsychotics for Irritability in Pediatric Autism: A Systematic Review and Network Meta-analysis. Journal of Child & Adolescent	This systematic review and network meta-analysis assessed the efficacy and safety of atypical antipsychotics in treating irritability. Eight trials comparing four interventions-risperidone, aripiprazole, lurasidone, and placebo in 878 patients, were included. Both risperidone and aripiprazole had significantly reduced ABC-I scores than placebo.	Does not change recommendation – could be added if section is updated in light of Hirsch.

	Psychopharmacology 2019;01 https://www.liebertpub.com/doi/abs/10.1089/cap.2018.0115?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=cap	Risperidone and aripiprazole were the two best drugs, with comparable efficacy and safety in paediatric ASD patients.	
8.2	Fung (2016) Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. Pediatrics 2016;137 Suppl 2(S124-35)	Forty-six RCTs were identified. Compared with placebo, three compounds resulted in significant improvement in ABC-I at the end of treatment. Risperidone and aripiprazole were found to be the most effective, with the largest effect sizes. N-acetylcysteine was the third compound. Although risperidone and aripiprazole have the strongest evidence in reducing ABC-I in youth with ASD, a few other compounds also showed significant efficacy with fewer potential side effects and adverse reactions in single studies.	Does not change recommendation.
8.2.1	Mechler (2018) Glutamatergic Agents in the Treatment of Compulsivity and Impulsivity in Child and Adolescent Psychiatry: a Systematic Review of the Literature. Zeitschrift fur Kinder-und Jugendpsychiatrie und Psychotherapie 2018;46(3):246-263	Search to Nov 2014 - 21 trials examining six glutamatergic substances in patients with obsessive-compulsive disorder, autism spectrum disorders, and attention deficit/hyperactivity disorder were included. Available data support the hypothesis that glutamatergic agents are of potential value in the treatment of compulsivity/impulsivity in children and adolescents. Based on the data reviewed, memantine and N-acetylcysteine suggest the best risk-benefit profile for future trials. Riluzole should primarily be further investigated in adults. Encompasses refs 204 and 205 from SIGN 145	Search dates of systematic review cover same range as SIGN 145 literature review. Exclude. Pilot study is not robust enough to support a recommendation. No action required.

	https://econtent.hogrefe.com/doi/10.1024/1422-4917/a000546?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov	See also RCT: • Wink (2018) A Randomized Placebo-Controlled Cross-Over Pilot Study of Riluzole for Drug-Refractory Irritability in Autism Spectrum Disorder https://link.springer.com/article/10.1007%2Fs10803-018-3562-5	
8.3	Sturman (2017) Methylphenidate for children and adolescents with autism spectrum disorder Cochrane Database of Systematic Reviews	Search to Nov 2016 identified four studies involving 113 children aged 5 to 13 years and comparing methylphenidate versus placebo.Two studies with five-year-old children were included as it was not possible to separate the data for those aged six years and above, and all other participants were in the target age range. In all of these studies, children took different doses of methylphenidate (low, medium or high) for one week and placebo for another week, and their caregivers (including parents, teachers and clinicians) rated their symptoms at the end of each week. All of the studies took place in the USA. Methylphenidate may improve hyperactivity, as assessed by parents and teachers, in the short term. Teachers also tended to report an improvement in children taking methylphenidate in relation to inattention, social interaction, repetitive behaviours, and overall ASD symptoms. Encompasses ref 206 in SIGN 145. http://dx.doi.org/10.1002/14651858.CD011144.pub2	Studies of just one week of therapy. Does not add anything new to the evidence and recommendation in SIGN 145. No action required.
8.4	Patra (2019) Atomoxetine for attention deficit hyperactivity disorder in children and adolescents with autism: A systematic review and meta-analysis. Autism research 2019;17	Three RCTs n=241 Atomoxetine had a benefit on improving parent-rated hyperactivity (standardized mean difference [SMD] = -0.73, 95% CI = -1.15 to -0.34) and parent-rated inattention (SMD = -0.53, 95% CI = -0.93 to -0.12) but the magnitude of effects is uncertain. However, atomoxetine was also associated with increased risk	Consider for update.

	https://onlinelibrary.wiley.com/doi/abs/10.1002/aur.2059	of non-serious adverse effects like nausea and vomiting, decreased sleep, and decreased appetite. Links to research recommendation in SIGN 145	
8.7.2 9.10. 2	Cai (2018) Systematic review and meta-analysis of reported adverse events of long-term intranasal oxytocin treatment for autism spectrum disorder. Psychiatry & Clinical Neurosciences 2018;72(3):140-151	Search to Jan 2017. Nasal discomfort (14.3%), tiredness (7.2%), irritability (9.0%), diarrhoea (4.5%), and skin irritation (4.5%) were the most common adverse events. None of these common adverse events was statistically associated with treatment allocation according to meta-analysis using pooled data (all p-values > 0.1). Five severe adverse events were reported, namely aggression (one in placebo, two in oxytocin) and seizures (one in placebo, one in oxytocin).	Consider for update.
8.7.2 9.10. 2	Ooi (2017) Oxytocin and Autism Spectrum Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pharmacopsychiatry 2017;50(1):5-13 https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0042-109400.pdf	12 RCTs identified to June 2015. Seven out of the 11 studies that examined social cognition reported improvements. One out of the four studies on restricted, repetitive behaviours, reported improvements following oxytocin administration. However, results from our meta-analyses suggest that oxytocin has no significant effect on these two domains. Findings on the effectiveness of oxytocin on ASD should still be considered tentative See also RCT: • Yamasue (2018) Effect of intranasal oxytocin on the core social symptoms of autism spectrum disorder: a randomized clinical trial https://www.nature.com/articles/s41380-018-0097-2	Consider for update.

	Section 9 Pharmcological interventions - adults		
8/9	Virgilio 2017 Cannabinoids in patients with autism spectrum disorders. Buenos Aires; Institute for Clinical Effectiveness and Health Policy (IECS): 2017	No available scientific evidence which would allow determining the effectiveness of cannabinoids use for the treatment of patients with autism spectrum disorders was found. The clinical practice guidelines consulted do not mention the use of this technology in autism spectrum disorders and no coverage policies considering its use were found. From CRD – no English language summary available.	Out of remit and no evidence. No action required.
Section 10 Service provision			
Nil			
Section 11 Provision of information			
	Boshoff (2018) Parents' voices: "Our process of advocating for our child with autism." A meta-synthesis of parents' perspectives. Child: Care, Health & Development 2018;44(1):147-160	The voices of 1,662 parents are presented describing the process of advocacy in the stages of seeking a diagnosis, seeking self education, and taking action. Results highlight the significant impact that positive experiences with first-line professionals have during the diagnosis process. See also: • Boshoff (2016) Parents' voices: 'why and how we advocate'. A meta-synthesis of parents' experiences of advocating for their child with autism spectrum disorder.	Unlikely to change recommendations. No action required.
Topic areas outwith or tangential to current guideline			
	Barahona-Correa (2018) Repetitive Transcranial Magnetic Stimulation for Treatment of Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Frontiers in Integrative Neuroscience 2018;12(27)	Transcranial Magnetic Stimulation (rTMS) is a technique for non-invasive neuromodulation. Four case-reports, seven non-controlled clinical trials, and 12 controlled clinical trials, comparing the effects of real TMS with waiting-list controls (n=6) or sham-treatment (n=6). Meta-analyses showed a significant, but moderate, effect on repetitive and stereotyped behaviours, social behaviour, and number of errors in executive function tasks, but not other outcomes.	Evidence not robust enough to support a recommendation. No action required.

		Insufficient quality of evidence to support offering TMS to treat ASD Links to research recommendation in SIGN 145	
	Xiong (2016) Hyperbaric oxygen therapy for people with autism spectrum disorder (ASD) Cochrane Database of Systematic Reviews http://dx.doi.org/10.1002/14651858.CD010922.pub2	Identified a single, small study of 60 children that evaluated high-pressure oxygen therapy for ASD. There was no evidence that high-pressure oxygen therapy improved social interaction, behavioural problems, speech or language communication, or mental function in children with ASD. However, children who received high-pressure (hyperbaric) oxygen therapy showed an increased occurrence of ear barotrauma events. The quality of the evidence is low. Insufficient to confirm that high-pressure oxygen is an effective treatment for individuals with ASD. Links to research recommendation in SIGN 145	Evidence not robust enough to support a recommendation. No action required.
	Postorino (2017) A Systematic Review and Meta-analysis of Parent Training for Disruptive Behavior in Children with Autism Spectrum Disorder. Clinical Child & Family Psychology Review 2017;20(4):391-402 https://link.springer.com/article/10.1007%2Fs10567-017-0237-2	Eight RCTs involving a total of 653 participants. Review summarises the essential elements of PT for disruptive behaviour in children with ASD and evaluates the available evidence for PT using both descriptive and meta-analytic procedures. Results support the efficacy of PT for disruptive behaviour in children with ASD, with a SMD of -0.59 [95% CI -0.88 to -0.30); p<0.001]. May link to SIGN 145 research recommendation on challenging behaviour?	Consider for update.
	Hourston (2017) Autism and Mind-Body Therapies: A Systematic Review. Journal of Alternative & Complementary Medicine 2017;23(5):331-339	Sixteen studies were selected for review; these studies tested interventions using mindfulness, meditation, yoga, Nei Yang Gong, and acceptance commitment therapy. Only three of the studies were randomsed controlled trials. Most studies were small and uncontrolled. Evidence for mind-body therapies for people with ASD	Insufficient evidence to support a recommendation. No action required.

		is limited and would benefit from larger randomised controlled trials. Links to research recommendation in SIGN 145	
	da Silva (2017) Oral health status of children and young adults with autism spectrum disorders: systematic review and meta-analysis. International Journal of Paediatric Dentistry 2017;27(5):388-398	Seven studies to Dec 2015. Prevalence of dental caries and periodontal disease in children and young adults with ASD can be considered as high, pointing to the need for oral health policies focused on these individuals.	Out of scope. No action required.
	Niemczyk (2018) Incontinence in autism spectrum disorder: a systematic review. European Child & Adolescent Psychiatry 2018;27(12):1523-1537	33 publications The published literature implies a higher prevalence of incontinence in children with ASD compared to typically developing children. Limitations and biases as inappropriate diagnostic criteria for ASD and incontinence, selected samples, or lack of control groups are reported. Incontinence symptoms are also reported as an adverse effect of medication in ASD. Due to methodological problems and definitional discrepancies in some publications, results have to be interpreted cautiously.	Out of scope and evidence is not robust. No action required.
Annex 3			
	Maher (2018) Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018;75(8):809-819	Exposure to hypertensive disorders of pregnancy may be associated with an increase in the risk of ASD and ADHD. These findings highlight the need for greater paediatric surveillance of infants exposed to HDP to allow early intervention that may improve neurodevelopmental outcome.	Consider for addition to Annex 3.
	Tick (2016)	Meta-analysis correlations for monozygotic twins (MZ) were almost perfect at 0.98 (95% confidence interval,	Sibling risk is already noted. No action required.

	Heritability of autism spectrum disorders: a meta-analysis of twin studies. Journal of Child Psychology & Psychiatry & Allied Disciplines 2016;57(5):585-95	0.96 to 0.99). The dizygotic (DZ) correlation, however, was 0.53 (95% CI 0.44to 0.60) when ASD prevalence rate was set at 5% (in line with the Broad Phenotype of ASD) and increased to 0.67 (95% CI 0.61 to 0.72) when applying a prevalence rate of 1%.Demonstrates that: (a) ASD is due to strong genetic effects; (b) shared environmental effects become significant as a function of lower prevalence rate; (c) previously reported significant shared environmental influences are likely a statistical artefact of over-inclusion of concordant DZ twins.	
	Jiang (2016) Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. Brain, Behavior, & Immunity 2016;58(165-172)	Search to March 2016 identified 15 studies. Maternal infection during pregnancy was associated with an increased risk of ASD in offspring (OR=1.13, 95% confidence interval (CI): 1.03 to 1.23), particularly among those requiring hospitalization (OR=1.30, 95% CI: 1.14 to 1.50).	Consider for addition to Annex 3.
	Wang (2017) The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders in children: a meta-analysis. Molecular Autism 2017;8(51)	Search to March 2017, 12 studies. Maternal use of folic acid supplements during pregnancy could significantly reduce the risk of ASD in children regardless of ethnicity, as compared to those women who did not supplement with folic acid See also: • Gao (2016) New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring Children - A Systematic Review • Castro (2016) Folic acid and autism: What do we know?	This is on prevention of ASD, outwith guideline remit.
	Brown (2017) The Association Between Antenatal Exposure to	Search to Jan 2016 Six studies. It remains unclear whether the association between first trimester SSRI exposure and autism that	NICE reviewed evidence on SSRIs to update NICE guideline 128. The panel

	Selective Serotonin Reuptake Inhibitors and Autism: A Systematic Review and Meta-Analysis. Journal of Clinical Psychiatry 2017;78(1):e48-e58	was present in the case-control studies even after adjustment for maternal mental illness is a true association or a product of residual confounding. Future studies require robust measurement of maternal mental illness prior to and during pregnancy. See also • Andrade (2017) Antidepressant Exposure During Pregnancy and Risk of Autism in the Offspring, Meta-Review of Meta-Analyses • Kobayashi (2016) Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis • Kaplan (2016) Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis	concluded that the evidence was not robust enough to inform guidance. No action required.
	Oldereid (2018) The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. Human Reproduction Update 2018;24(3):320-389	Higher paternal age is probably associated with an increase in autism/ASD. Moderate certainty of evidence (GRADE⊕⊕⊕○)	This is already covered in the guideline. No action required.
	Loomes (2017) What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. Journal of the American Academy of Child & Adolescent Psychiatry 2017;56(6):466-474	Meta-analysis of prevalence studies conducted since the introduction of the DSM-IV and the ICD-10. 54 studies. Of children meeting criteria for ASD, the true male-to-female ratio is not 4:1, as is often assumed; rather, it is closer to 3:1. There appears to be a diagnostic gender bias, meaning that girls who meet criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis.	This is already covered in the guideline. No action required.

Section 3: Consultation feedback

Former members of the guideline development group for SIGN 145 were invited to comment on the report and the proposed areas for update.

Reviewer	Comments
Dr Magnus Cormack, Consultant Clinical Psychologist, Devon	There's some interesting research but nothing from the sections I covered that warrants an update or change in opinion.
Professor Karen MacKenzie, Clinical Psychologist, Northumbria University	The two main areas that would have relevance for me would be screening and identification (and it appears the new evidence wouldn't really change the current recommendations) and other interventions (exercise and parenting interventions). The latter is noted as being outwith or tangential to the main remit of SIGN 145 and so, for me the only potential area for update would be in relation to exercise interventions. This wouldn't seem to justify an update on its own, but if there were a number of other areas that the group felt were also important to update then it would be helpful to include exercise interventions.
Dr Claire Moir, GP Principal, Mill Clinic, Dundee	4.1.6 - suicidal ideation is a common feature in mental health presentations and the guideline already says healthcare professionals should be aware of indicators of ASD in those patients presenting with other conditions. Evidence appears weak and I am not sure this adds anything to current guideline. 4.1.6 Gender dysphoria - this is already in the guideline but is currently a very hot topic. Could we simply review the new studies to add weight to current guideline findings? 4.6 - Prognosis - progression found to be stable and new research supports this. Second study finds variability which has already been noted. This new evidence is supportive but may be saying the same thing as the current guideline, so may not be relevant to update on basis of this alone. 6.3.5 -OT- this is really not my area of expertise but appears to be quite positive. It does appear to feed in to the research above re prognosis in that interventions should focus on those that improve adaptive functioning and quality of life. Looks relevant to include.

	6.4 - Omega-3 fatty acids- we already suggest no benefit but I am not sure if this is something patients and parents ask dieticians about a lot. It could strengthen recommendation so possibly yes include if dietitians are asked about supplements a lot. 6.5 - Exercise- to me this looks important and possibly quite good evidence so I would review this for inclusion in guideline. 8.2 Aripirazole- could this just be an addition to the current recommendation rather than full rewrite? 8.4 - Atomoxetine - may be worth adding this as it is a fairly well tolerated drug and there are very limited drug options. 8.7 - Oxytocin - this evidence only seems to support the current guideline so I do not think a guideline review is needed just for this Parent training - this appears to be used in practice and if findings are that it is useful this would be relevant to add to the guideline Maternal high blood pressure and infection - I think this should go in to Annex 3 as an aide memoire to consider these factors and be more alert when reviewing child development.
Marion Rutherford, Senior Research Fellow, Autism ACHIEVE Alliance, Queen Margaret University	The areas where it might be helpful to have an updated evidence based statement/position (in my opinion) are: 4.1.6 Gender dysphoria, suicidality and ASD 4.6 Prognostic indicators 6.3.5 Sensory Integration 6.4 Omega 3 I do not see that there is currently a need to take up a guideline slot for this update.
Dr Jennifer Shields, Principal Educator – Autism NHS Education for Scotland	I agree we may not need a guideline slot this time, but at the seven-year mark there may be quite a bit of evidence which will need more thorough consideration. There's also the new SIGN guideline for prenatal alcohol exposure. I feel that these kids are often referred under FASD/ADHD so it may be prudent to include a note somewhere that SIGN 156 exists now.