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A systematic review with meta-analysis of different models of intervention for pre-school autism: study protocol

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ABSTRACT

Aim: The aims of our study are to: i) conduct a systematic review of the intervention literature in preschool autism spectrum disorder (ASD), including type of intervention that is tested and classification of outcome measures used; ii) to undertake a meta-analysis of the studies, allowing for the first time the comparison of different approaches to intervention using comparative outcomes.

Background: There are a number of alternative modalities of intervention for preschool ASD in use with different theoretical background and orientation, each of which tend to use different trial designs and outcome measures; and there has been no comparative review to date across intervention modality in order to inform clinical decisions. There is at this time an urgent need for comprehensive systematic review and meta-analyses of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for pre-school interventions in the disorder.

Design and methods: We will perform a systematic review of RCTs for preschool children with ASD, along with a meta-analysis of qualifying studies across intervention modality. We will classify the interventions for preschool ASD under three models; behaviour, multi-modal developmental, and communication-focused. Firstly, we will perform a systematic review. Then, we will conduct a meta-analysis by comparing the three models with various outcomes using an inverse variance method. We will synthesize each outcome of the studies for the three models using standardized mean differences.

Discussion: This study will identify each interventions strengths and weaknesses. This study may also reveal what points are lacking among the current intervention programmes for children with ASD. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

INTRODUCTION

Recent epidemiological studies estimate a prevalence of 1:100 for autism spectrum disorder (ASD) [1], which is a surprising increase over rates reported in the past [2]. There has been increasing interest in developing effective interventions for young children with ASD, since the evidence suggests that early intervention programmes are indeed beneficial for children with ASD, often improving developmental functioning and decreasing maladaptive behaviours and symptom severity [3], and also can improve outcomes in later years for most individuals [4].

An increasing volume of published trials of psychosocial intervention programmes for preschool ASD have been seen in recent years. These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism; iii) multimodal interventions targeted across areas of autistic children's development. In addition, an increasing number of these studies have followed CONSORT guidelines [5], and some meta-analyses and systematic reviews about intervention programmes for preschool children have been published [6,7,8,9,10,11]. These meta-analyses and systematic reviews focused exclusively on one or other of these groups of intervention styles; there has been no systematic review or meta-analysis of studies comparing results from different types of intervention approach from the viewpoint of the three models. For clinicians and commissioners this poses a difficulty in making general choices in a field containing often strong and partisan claims of effect from different traditions of intervention. Related to this, there has been great variation in endpoint measures used in these reported studies, making comparison of effects difficult. Specifically, there has been variation in whether endpoints have been framed in terms of autism symptom

outcomes, non autism-specific outcomes, or intermediate developmental endpoints; and these latter two have often been reported as if they were surrogate endpoints for autism-specific symptoms or disorder. We think that these considerations indicate the need for a more comprehensive review of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder. In this study, we will investigate it by comparing three major types of interventions with various outcomes.

We will undertake a systematic review and a meta-analysis of RCTs for preschool children with ASD. Recently many RCTs for children with ASD have been emerged as sufficient as to perform meta-analyses. RCT methodology has been identified as the gold standard in efficacy research [12,13]. In addition, meta-analyses of RCTs is the top hierarchy of evidence based medicine [14]. Thus, the findings of this study will be very strong evidence about interventions for children with ASD. We classify the interventions for preschool children with ASD under the three models; i.e. behaviour model, developmental model, and communication-focused model. Understanding the mechanisms that underlie this attenuation of treatment effects and how these can be overcome is one current challenge [15]. This study will reveal which type of interventions is the most effective to various kinds of treatment factors respectively. Its findings will guide us to develop new types of interventions to overcome the attenuation of treatment effects in the core symptoms of autism. It will contribute to the appropriate choices of the interventions for children with ASD for their families, clinicians, and the policymakers.

The objective of our study is to: i) conduct a systematic review of all the preschool intervention literature in ASD, including the type of intervention that is being tested and

classification of outcome measures used; ii) to undertake a meta-analysis of methodologically adequate studies using the Cochrane tool, which will allow for the first time comparison of different approaches to intervention on comparative outcome measures.

METHODS

Types of studies

We will include randomized controlled trials and subject these to a rating on quality criteria.

Types of participants

Participants comprise preschool children with a diagnosis of autism spectrum disorder (ASD) aged 0 to 6.

Types of interventions

We classify interventions for preschool ASD in three groups; i) behavioural interventions – based essentially on learning theory and on applied behaviour analysis; ii) communication-focused interventions, targeting social communication impairment, as the core symptom of autism; iii) multimodal developmental interventions targeting a range of aspects of children's development.

Types of outcome measures

A feature of this review is that we will systematically classify the various outcome measures used within recent intervention trials into the following categories:

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in Diagnostic and Statistical Manual of Mental Disorders-Ⅳ-TR [16] and the definitional symptoms of the disorder and key indicators of psychopathology.

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are IQ and cognitive development.

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples are: measures of joint attention, parent-child interaction, imitation ability, symbolic play, social communication in an interactive setting, receptive language, expressive language.

Electronic searches

We will do a systematic review of the published work according to the PRISMA statement [17]. Relevant studies will be identified by searching the following data sources: PsycINFO (from 1956 to January, 2011), Medline via Ovid (from 1950 to January, 2011), ERIC (from 1950 to January, 2011) and the Cochrane database.

We will use the following search terms to search all trials registers and databases: “autism” , “autism spectrum disorder”, “ASD”, “high function autism”, “high function ASD”, “Asperger syndrome”, “pervasive developmental disorder”, “PDDNOS”, “intervention”, “communication”, "interpersonal", "speech", "interaction", "synchrony", “relationship”, “language”, “social” and “development”, "behavior therapy", "intensive behavioral intervention". Their search will be limited by age group from 1 to 6 years old and “randomized controlled trial.” This search strategy has been peer-reviewed by a librarian of University of Manchester.

Validity assessment

Two of the authors, Y.T., Y.H. independently will review abstracts of potentially the relevant studies. This will be followed by a consensus discussion with J.G. The quality of the RCTs will be coded independently by Y.T. and Y.H. and disagreement will be resolved by consensus discussions.

Searching other resources

Reference lists from identified trials and review articles will be manually scanned to identify any other relevant studies. The clinicalTials.gov and the Cochrane Library

website will be also searched for randomized trials that were registered as completed but not yet published.

Data collection and analysis

Selection of studies

Inclusion:

1. Participants comprise preschool children with a diagnosis of ASD or pervasive developmental disorder (PDD).

2. Randomized controlled trials

3. Interventions delivered to the parents/guardians and/or directly to the child, by special educators, teachers, speech pathologists, psychologists, or other allied health professional students will be included.

4. Studies carried out while the children were at a preschool age between 0 and 6 years.

5. The control group will be those who did not received early intervention for autism.

6. Studies judged to be in low risk of bias according to the Cochrane Collaboration tool for assessing risk of bias

Exclusion:

1. The study was not primary research on preschool autism.

2. The study did not assess a cognitive/behavioural intervention for preschool autism.

3. The study did not report adequately on any measurable data for health related outcomes relevant to the review.

4. The study design was not a randomized controlled trial.

5. The intervention used alternative medicine.

6. The intervention was pharmacological one.

7. The intervention was not classified into behavioural, multimodal developmental or communication-focused model.

8. The control group received some early intervention for children with autism.

9. Studies judged to be in high risk of bias according to the Cochrane Collaboration tool for assessing risk of bias

All citations sourced from the search strategy will be transferred to EndNote, a reference management database software. Initial screening of titles and abstracts by an experienced research fellow (YT) will eliminate all those citations obviously irrelevant to the topic, for example, prevalence studies, studies not relating to autism spectrum disorders, single case studies. Thereafter, two review authors (YT and YH) will assess and select studies for inclusion from the group of superficially relevant studies. In the event of a disagreement, resolution will be reached in discussion with the third author (JG), if necessary following inspection of the full paper.

Data extraction and management

YT and YH will independently extract data from selected trials using a specially designed data extraction form. Extracted data will consist of methods (dose and frequency of intervention); diagnostic description of participants, and type of intervention, including target, intensity, duration and method of application (parent-mediated, therapist, school-based etc.). Data will be extracted independently by two review authors (YT and YH) and disagreements will be resolved by negotiation with a third author (JG).

Assessment of risk of bias in included studies

Risk of bias will be assessed by two independent review authors (YT and YH) and disagreements will be resolved by negotiation with a third review author (JG). We will use the Cochrane Collaboration tool for assessing risk of bias in these areas [18]. The assessed risk of bias in studies will include in the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other sources of bias. The process will involve recording the appropriate information for each study (for example describing the method used to conceal allocation in detail) and evaluating whether there is risk of bias in that area (for example, was allocation adequately concealed). We will allocate studies to the three categories according to our judgment of each area or potential risk of bias: A. Low risk of bias; B. Moderate (or unclear) risk of bias; C. High risk of bias.

Measures of treatment effect

The categories of outcome measure differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims for the first time to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses, comparing type of intervention model effectiveness for each outcome using a standardized mean difference. This is a novel approach for this field.

Dealing with missing data

Missing data will be assessed for each individual study. Where a loss of significant quantities of participant data is reported such that the review authors agree that the conclusions of the study are compromised, trial authors will be contacted. If no reply is forthcoming or full data are not made available, these studies will not be included in the final analysis. For included studies reporting drop-out, we will report the number of participants included in the final analysis as a proportion of those participants who began the intervention. Reasons for missing data will be reported. The extent to which the results of the review could be altered by the missing data will be assessed and discussed. If summary data are missing, trial authors will be contacted. If no reply is forthcoming or the required summaries are not made available, the authors will include the study in the review and assess and discuss the extent to which its absence from meta-analysis affects the review results.

Assessment of heterogeneity

Consistency of results will be assessed visually and by a Chi2 test. If the meta-analysis includes only a small number of studies, or where studies have small sample sizes, a P value of 0.10 will be applied for statistical significance. In addition, since Chi2 can have low power when only few studies or studies of a small sample size are available, we will use the I2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis (Higgins 2008).

Assessment of reporting biases

If sufficient studies are found, funnel plots will be drawn to investigate any relationship between effect size and sample size. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. If a relationship is identified, clinical diversity of the studies will be further examined as a possible explanation. Every attempt will be made to obtain unpublished data and data from conference proceedings.

Data synthesis

Data synthesis will be performed using Review Manager version 5.1 (Cochrane Collaboration software). We will assess continuous and binary data. Assuming that two or more studies that are suitable for inclusion are found, and that the studies are

considered to be homogenous, a meta-analysis will be performed on the results. The categories of outcome measure mentioned above differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses, since we do not assume that each study is estimating exactly the same quantity. We will compare the types of intervention model effectiveness for each outcome using a standardized mean difference.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses and meta-regression and where no significant heterogeneity of effect sizes is found, these will be pooled to calculate a final effect size. While these analyses may enable us to hypothesize as to possible causes of differences between studies' findings, some heterogeneity is likely to remain, and any statistical analysis will be accompanied by a narrative synthesis.

Subgroup analysis will be undertaken if clinically different interventions are identified, or there are clinically relevant differences between participant groups. Anticipated clinically relevant differences are:

1. intervention delivery type (e.g. therapist, parent-mediated, school-based) and length
2. intervention target skill (e.g. Theory of Mind as a whole, joint attention, emotion recognition, false belief understanding)

3. participant age (e.g. preschool, young children, adolescents, adults), IQ (low versus normal or high), specific diagnosis and verbal ability.

Sensitivity analysis

Relevant subgroups analyses will include:

·Severity of autism at baseline. This is a crucial element in evaluating autism studies.

·SES and other demographic variables. Sampling bias and external validity of studies is an important consideration.

·Age of child

·Type of intervention (our 3 groups as above)

·Parent-mediated vs child-mediated intervention delivery. A key distinguishing point between different studies in the area.

·Cognitive ability at baseline.

Sensitivity analysis will be conducted to assess the impact of study quality on the results of the meta-analyses. For example, we will test to see if studies with high rates of loss to follow up or inadequate blinding are more likely to show positive outcomes and also to assess the impact of imputing missing data.

DISCUSSION

We believe that the findings of this systematic review and meta-analysis will have important implications for both clinical practice and research. Meta-analysis of randomized controlled trials of the interventions for preschool children with ASD will provide the most reliable basis for the decisions of early interventions for them. Analyses as to the three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD. This study will provide information about which kind of intervention has strength points and weak points, and what are those strength points and weak points are. This study may also reveal what points are lacking among the current intervention programmes for children with ASD. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

Authors' contribution YT and JG contributed to draft the protocol and develop a search strategy. YT also drafted this manuscript. RE contributed to provide statistical advice for the design and the analysis. All authors read and approved the final manuscript.

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Competing interests None.

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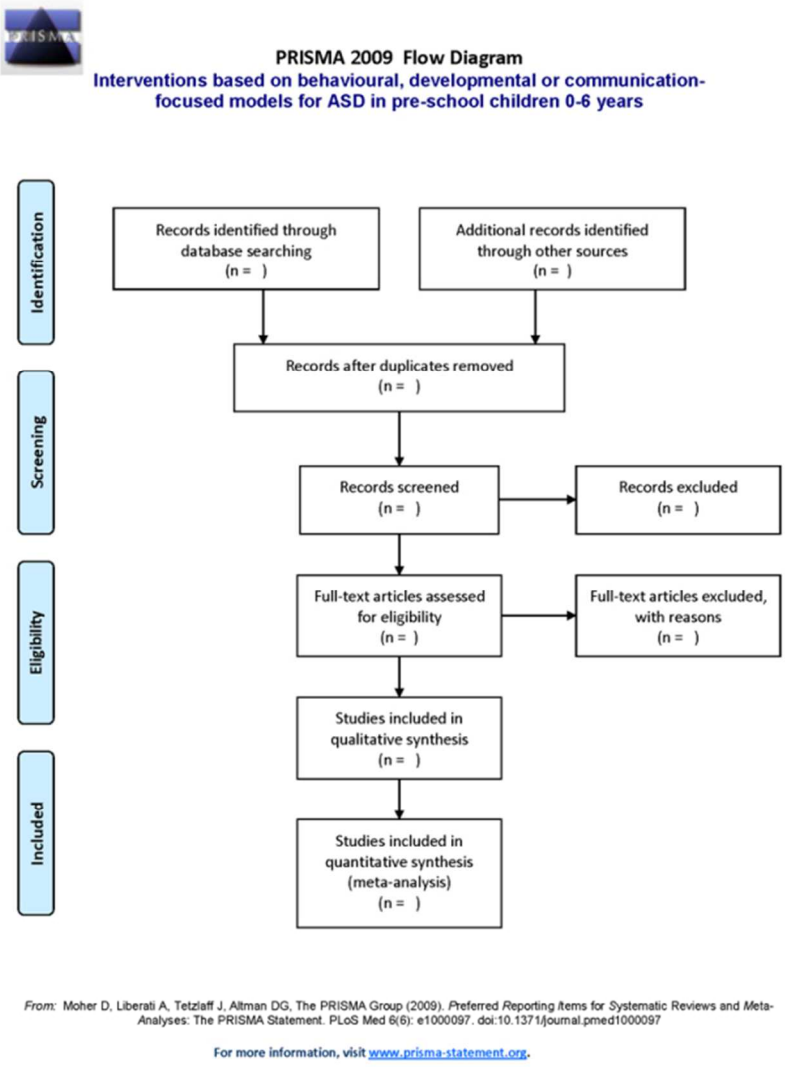

Caption: Figure 1
Legend: Flow diagram of this study

A systematic review with meta-analysis of comprehensive interventions for preschool children with autism spectrum disorder: study protocol

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ABSTRACT

Introduction: The aims of our study are to: i) conduct a systematic review of the intervention literature in preschool autism spectrum disorder (ASD), including type of intervention that is tested and classification of outcome measures used; ii) to undertake a meta-analysis of the studies, allowing for the first time the comparison of different approaches to intervention using comparative outcomes. There are a number of alternative modalities of intervention for preschool ASD in use with different theoretical background and orientation, each of which tend to use different trial designs and outcome measures. There is at this time an urgent need for comprehensive systematic review and meta-analyses of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder.

Methods and analysis: We will perform a systematic review of RCTs for preschool children with ASD aged 0 to 6, along with a meta-analysis of qualifying studies across intervention modality. We will classify the interventions for preschool ASD under three models; behaviour, multi-modal developmental, and communication-focused. Firstly, we will perform a systematic review. Then, we will conduct a meta-analysis by comparing the three models with various outcomes using an inverse variance method in a random effect model. We will synthesize each outcome of the studies for the three models using standardized mean differences.

Dissemination and ethics: This study will identify each intervention's strengths and weaknesses. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

Trial registration:

http://www.crd.york.ac.uk/prospero/register_new_review.asp?RecordID=1349&UserID

=230 (Registration No. CRD42011001349)

INTRODUCTION

Recent epidemiological studies estimate a prevalence of 1:100 for autism spectrum disorder (ASD) [1], which is a surprising increase over rates reported in the past [2]. There has been increasing interest in developing effective interventions for young children with ASD, since the evidence suggests that early intervention programmes are indeed beneficial for children with ASD, often improving developmental functioning and decreasing maladaptive behaviours and symptom severity [3], and also can improve outcomes in later years for most individuals [4].

An increasing volume of published trials of psychosocial intervention programmes for preschool ASD have been seen in recent years. These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism; iii) multimodal interventions targeted across areas of autistic children's development. In addition, an increasing number of these studies have followed CONSORT guidelines [5], and some meta-analyses and systematic reviews about intervention programmes for preschool children have been published; e.g. [6-8]. These meta-analyses and systematic reviews focused exclusively on one or other of these groups of intervention styles; there has been no systematic review or meta-analysis of studies comparing results from different types of intervention approach from the viewpoint of the three models. For clinicians and commissioners this poses a difficulty in making general choices in a field containing often strong and partisan claims of effect from different traditions of intervention. Related to this, there has been great variation in endpoint measures used in these reported studies, making comparison of effects difficult. Specifically, there has been variation in whether endpoints have been framed in terms of autism symptom outcomes, non autism-specific outcomes, or intermediate developmental endpoints; and these latter two have often

been reported as if they were surrogate endpoints for autism-specific symptoms or disorder. We think that these considerations indicate the need for a more comprehensive review of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder. In this study, we will investigate it by comparing three major types of interventions with various outcomes.

We will undertake a systematic review and a meta-analysis of RCTs for preschool children with ASD. Recently many RCTs for children with ASD have been emerged as sufficient as to perform meta-analyses. RCT methodology has been identified as the gold standard in efficacy research [9]. In addition, meta-analyses of RCTs is the top hierarchy of evidence based medicine [10]. Thus, the findings of this study will be very strong evidence about interventions for children with ASD. Howlin et al. are asserting that there are three main strands of early interventions for children with ASD): programs with a particular emphasis on the use of behavioural principle to improve learning and behaviour; those that have a specific focus on communication; and those in which developmental/educational strategies have been employed [11]. In this study, we named those strands as behavioural, communication-focused, and multimodal developmental interventions, respectively. Understanding the mechanisms that underlie this attenuation of treatment effects and how these can be overcome is one current challenge [12]. This study may reveal each type of the intervention's strong and weak points to various kinds of treatment factors respectively. Its findings will guide us to develop new types of interventions to overcome the attenuation of treatment effects in the core symptoms of autism. It will contribute to the appropriate choices of the interventions for children with ASD for their families, clinicians, and the policymakers.

The objective of our study is to: i) conduct a systematic review of all the preschool intervention literature in ASD, including the type of intervention that is being tested and classification of outcome measures used; ii) to undertake a meta-analysis of methodologically adequate studies using the Cochrane tool, which will allow for the first time comparison of different approaches to intervention on comparative outcome measures.

METHODS

Types of studies

We will include randomized controlled trials and subject these to a rating on quality criteria.

Types of participants

Participants comprise preschool children aged 0 to 6 with a diagnosis of ASD as below.

Diagnostic and statistical Manual of Mental Disorders-Ⅳ-Text Revision (DSM-Ⅳ-TR) [13]

- Autistic disorder
- Asperger disorder
- Pervasive developmental disorder not otherwise specified (PDD-NOS)

International Classification of Diseases-10 (ICD-10) [14]

- Childhood autism
- Asperger syndrome, atypical autism
- Other pervasive developmental disorders
- Pervasive developmental disorders, unspecified.

Types of interventions

We classify interventions for preschool ASD in three groups; i) behavioural interventions – based essentially on learning theory and on applied behaviour analysis; ii) communication-focused interventions, targeting social communication impairment, as the core symptom of autism; iii) multimodal developmental interventions targeting a range of aspects of children's development.

Types of outcome measures

A feature of this review is that we will systematically classify the various outcome measures used within recent intervention trials into the following categories:

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in DSM-Ⅳ-TR and the definitional symptoms of the disorder and key indicators of psychopathology (e.g. the autism Diagnostic Observation Schedule-Generic [15] will be used for these outcomes.).

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are IQ and cognitive development (e.g. the Wechsler Preschool and Primary Scale of Intelligence third edition [16] will be used for these outcomes.).

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples (along

with appropriate measures) are: measures of adaptive behavior (the Vineland Adaptive Behavior Scale [17]), joint attention (the Early Social Communication Scales [18]), imitation ability (the Imitation Battery [19]), symbolic play (the Communication and Symbolic Behavior Scales Developmental Profile [20]), parent-child interaction (the Dyadic Communication Measure for Autism [21]), receptive language (the MacArthur-Bates Communicative Development Inventory (MCDI [22])), expressive language (MCDI [22]).

Electronic searches

We will do a systematic review of the published work according to the PRISMA statement [23]. Relevant studies will be identified by searching the following data sources: PsycINFO (from 1956 to January, 2011), Medline via Ovid (from 1950 to January, 2011), ERIC (from 1950 to January, 2011) and the Cochrane database.

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Validity assessment

Two of the authors, Y.T., Y.H. independently will review abstracts of potentially the relevant studies. This will be followed by a consensus discussion with J.G. The quality

of the RCTs will be coded independently by Y.T. and Y.H. and disagreement will be resolved by consensus discussions.

Searching other resources

Reference lists from identified trials and review articles will be manually scanned to identify any other relevant studies. The clinicalTials.gov and the Cochrane Library website will be also searched for randomized trials that were registered as completed but not yet published.

Data collection and analysis

Selection of studies

Inclusion:

1. Participants comprise preschool children with a diagnosis of ASD or pervasive developmental disorder (PDD).

2. Randomized controlled trials

3. Interventions delivered to the parents/guardians and/or directly to the child, by special educators, teachers, speech pathologists, psychologists, or other allied health professional students will be included.

4. Studies carried out while the children were at a preschool age between 0 and 6 years.

Exclusion:

1. The study was not primary research on preschool autism.

2. The study did not assess a cognitive/behavioural intervention for preschool autism.

3. The study design was not a randomized controlled trial.

4. Alternative or complementary medicine was used as the main intervention of the study.

5. The intervention was pharmacological one.

6. The intervention was not classified into behavioural, multimodal developmental or communication-focused model.

7. The control group received a specific early intervention programme for children with autism which was not a usual treatment provided by their local services.

8. Studies judged to be in high risk of bias according to the Cochrane Collaboration tool for assessing risk of bias

All citations sourced from the search strategy will be transferred to EndNote, a reference management database software. Initial screening of titles and abstracts by an experienced research fellow (YT) will eliminate all those citations obviously irrelevant to the topic, for example, prevalence studies, studies not relating to autism spectrum disorders, single case studies. Thereafter, two review authors (YT and YH) will assess and select studies for inclusion from the group of superficially relevant studies. In the event of a disagreement, resolution will be reached in discussion with the third author (JG), if necessary following inspection of the full paper.

Data extraction and management

YT and YH will independently extract data from selected trials using a specially designed data extraction form. Extracted data will consist of methods (dose and frequency of intervention); diagnostic description of participants, and type of intervention, including target, intensity, duration and method of application (parent-mediated, therapist, school-based etc.). Data will be extracted independently by two review authors (YT and YH) and disagreements will be resolved by negotiation with a third author (JG).

Assessment of risk of bias in the studies

Risk of bias will be assessed by two independent review authors (YT and YH) and disagreements will be resolved by negotiation with a third review author (JG). We will use the Cochrane Collaboration tool for assessing risk of bias in these areas [24]. The assessed risk of bias in studies will include in the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other sources of bias. The process will involve recording the appropriate information for each study (for example describing the method used to conceal allocation in detail) and evaluating whether there is risk of bias in that area (for example, was allocation adequately concealed). We will allocate studies to the three categories according to our judgment of each area or potential risk of bias: A. Low risk of bias; B. Moderate (or unclear) risk of bias; C. High risk of bias. Whether the studies should be included for the analyses or not will be judged individually based on the results of the risk of bias assessments.

Measures of treatment effect

Continuous data

Continuous data will be analysed on the basis that the means and standard deviations are available and that there is no clear evidence of skew in the distribution.

Dealing with missing data

Missing data will be assessed for each individual study. Where a loss of significant quantities of participant data is reported such that the review authors agree that the conclusions of the study are compromised, trial authors will be contacted. If no reply is forthcoming or full data are not made available, these studies will not be included in the

final analysis. For included studies reporting drop-out, we will report the number of participants included in the final analysis as a proportion of those participants who began the intervention. Reasons for missing data will be reported. The extent to which the results of the review could be altered by the missing data will be assessed and discussed. If summary data are missing, trial authors will be contacted. If no reply is forthcoming or the required summaries are not made available, the authors will include the study in the review and assess and discuss the extent to which its absence from meta-analysis affects the review results.

Assessment of heterogeneity

Consistency of results will be assessed visually and by chi-square tests [25]. In addition, since chi-square can have low power when only few studies or studies of a small sample size are available [26], we will use the I^2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis [27].

Assessment of reporting biases

If sufficient studies are found, funnel plots will be drawn to investigate any relationship between effect size and sample size. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. If a relationship is identified, clinical diversity of the studies will be further examined as a possible explanation. Every attempt will be made to obtain unpublished data and data from conference proceedings.

Data synthesis

Data synthesis will be performed using Review Manager version 5.1 (Cochrane Collaboration software). We will assess continuous and binary data. Assuming that two or more studies that are suitable for inclusion are found, and that the studies are considered to be homogenous, a meta-analysis will be performed on the results. The categories of outcome measure mentioned above differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method in a random effect model[27]. We will compare the types of intervention model effectiveness for each outcome using a standardized mean difference.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses and meta-regression and where no significant heterogeneity of effect sizes is found, these will be pooled to calculate a final effect size. While these analyses may enable us to hypothesize as to possible causes of differences between studies' findings, some heterogeneity is likely to remain, and any statistical analysis will be accompanied by a narrative synthesis.

Subgroup analysis will be undertaken if clinically different interventions are identified, or there are clinically relevant differences between participant groups. Anticipated clinically relevant differences are:

1. intervention delivery type (e.g. therapist, parent-mediated, school-based) and length
2. intervention target skill (e.g. Theory of Mind as a whole, joint attention, emotion recognition, false belief understanding)
3. participant age (e.g. preschool, young children, adolescents, adults), IQ (low versus normal or high), specific diagnosis and verbal ability.

Relevant subgroup analyses will also include:

·Severity of autism at baseline. This is a crucial element in evaluating autism studies.

·Social economic status and other demographic variables. Sampling bias and external validity of studies is an important consideration.

·Age of child

·Type of intervention (our 3 groups as above)

·Parent-mediated (directing parents to train their children, not training the children directly) vs. child-mediated (training the children directly) intervention delivery

·Cognitive ability at baseline

Sensitivity analysis

Sensitivity analysis will be conducted to assess the impact of study quality on the results of the meta-analyses. For example, we will test to see if studies with high rates of loss to follow up or inadequate blinding are more likely to show positive outcomes and also to assess the impact of imputing missing data.

DISCUSSION

We believe that the findings of this systematic review and meta-analysis will have important implications for both clinical practice and research. Meta-analysis of RCTs of the interventions for preschool children with ASD will provide the most reliable basis for the decisions of early interventions for them. Analyses as to the three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD. This study will provide information about which kind of intervention has strength points and weak points, and what are those strength points and weak points are. This study may also

suggest what kinds of elements future intervention programmes for children with ASD should have. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits. Anticipated challenges in synthesize the literature exist. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We do not assume that each study is estimating exactly the same quantity. Thus, we will use random effect models for the analyses [27]. In addition, the durations of the interventions will be different among the studies included in this study. We will synthesize the data regardless of the durations of the interventions, and will discuss the diversity of the durations in our paper.

Authors' contribution YT and JG contributed to draft the protocol and develop a search strategy. YT also drafted this manuscript. RE contributed to provide statistical advice for the design and the analysis. All authors read and approved the final manuscript.

Acknowledgement We thank Claire Hodkinson for peer-reviewing the search strategy of this study.

Competing interests None.

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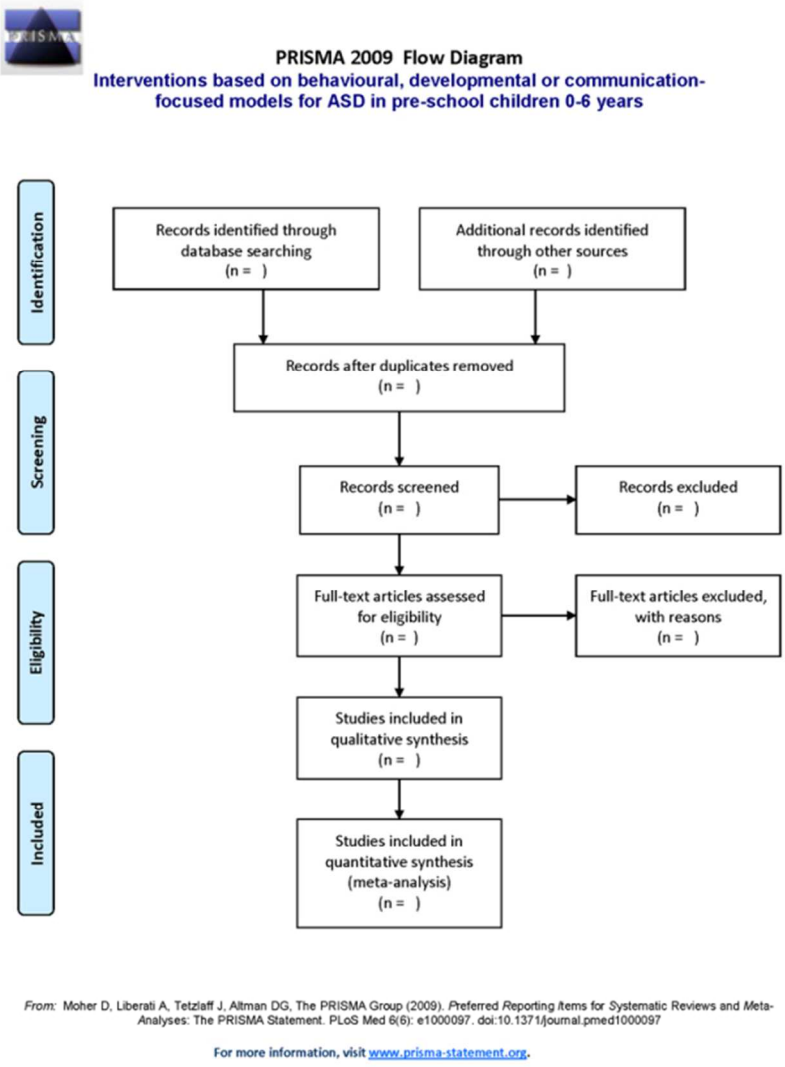

Caption: Figure 1
Legend: Flow diagram of this study

December 23th , 2011

The BMJ Open Editorial Office
Dear Editor,
RE: BMJ Open - Decision on Manuscript ID bmjopen-2011-000679

Thank you very much for your editorial work on our manuscript entitled "A systematic review with meta-analysis of different models of intervention for pre-school autism: study protocol". We also thank Dr. Iliana Magiati and Dr. Sigmund Eldevik for helpful suggestions and constructive criticisms. We took into account their comments in our revised manuscript.

Responses to the managing editor's comments:

You may wish to consider registering your systematic review with the PROSPERO Registry: http://www.crd.york.ac.uk/prospero/

This registration number can then be included in your abstract.

Please structure the abstract: Introduction; Methods and analysis; Ethics and dissemination. Registration details should be included as a final section, if appropriate.

We changed the Abstract structure and added the PROSPERO registry URL and the registration number as follows.

Trial registration:

http://www.crd.york.ac.uk/prospero/register_new_review.asp?RecordID=1349&UserID=230 (Registration No. CRD42011001349)

Responses to Dr. Iliana Magiati's comments:

Firstly, I am personally not aware of any systematic reviews or meta-analyses publishing their methodology/ protocol prior to publishing the actual study's findings. I have to admit that I wonder how useful it would be for the reader to read the proposed protocol of a meta-analysis without the actual findings of that particular meta-analysis. Published study protocols primarily present in detail the intervention protocol of an RCT trial and as such are potentially interesting and important, as often clinicians and professionals wish to find out more details about the theoretical background, structure, content and approach employed in different intervention outcome studies. I am also aware of a few study protocols on prospective longitudinal cohort studies, but not of

meta-analyses. I am thus not sure that reading about the inclusion and exclusion criteria and proposed methodological process of a meta-analysis serves a similarly useful function. As a reader, what I really want to read – and I think most readers would agree- is the actual results of such a meta-analysis. The information presented in this paper could be concisely presented in the Methods section of such a publication. Clearly, this is the Editor's decision to make, but as a reviewer I question the significance of publishing a study protocol of a systematic review.

We take a different view to the reviewer. It is now common practice to lodge protocols prior to studies of this kind. For example, the Cochrane Library publishes research protocols for new systematic reviews and meta-analysis. They mention the reasons they publish protocols of systematic review and meta-analysis as follows.

"All research should be carried out according to a pre-defined plan. Cochrane researchers use the protocol to describe the proposed approach for a systematic review. It outlines the question that the review authors are addressing, detailing the criteria against which studies will be assessed for inclusion in the review, and describing how the authors will manage the review process. Protocols contain information that defines the health problem and the intervention under investigation, how benefits and harms will be measured, and the type of appropriate study design. The protocol also outlines the process for identifying, assessing, and summarizing studies in the review. By making this information available the protocol is a public record of how the review authors intend to answer their research question."

http://www.thecochranelibrary.com/view/0/AboutCochraneSystematicReviews.html

We think the same principle would hold for BMJ Open.

TITLE

I think the title can be more precise, accurate and describe with more exact terms what will be done (i.e. comprehensive pre-school interventions for pre-school children with Autism Spectrum Disorders).

We revised the title according to your suggestion.

"A comprehensive systematic review with meta-analysis of pre-school interventions for children with autism spectrum disorder: study protocol"

ABSTRACT

Upon revision of the manuscript, the abstract also needs to be revised to be more accurate, specific and clear. Age range of children for example needs to be included in the abstract.

We have changed the description in the abstract as below.

We will perform a systematic review of RCTs for preschool children with ASD aged 0 to 6.

Non-specific terminology such as "points are lacking" also needs to be avoided.

We have changed the sentence as below.

This study may also suggest what kinds of components the future intervention programmes for children with ASD should have.

INTRODUCTION

The description of the "three models" could improve by clearly defining/ describing these models, including some key references for these models. I will also come back to this issue in the Methods section.

Our definition follows Howlin et al. are asserting that there are three main strands of early interventions for children with ASD): programs with a particular emphasis on the use of behavioural principle to improve learning and behaviour; those that have a specific focus on communication; and those in which developmental/educational strategies have been employed (Howlin et al., 2009). In this study, we named those strands as behavioural, communication-focused, and multimodal developmental interventions, respectively.

I also believe, given the challenges and limitations of current research, that terms such as "this study will reveal which type of intervention is the most effective" are too strong to be supported by evidence and need to be revised.

We accept this and have changed text to "This study may reveal each type of the intervention's strong and weak points."

METHODS

Types of studies – RCTs continue, unfortunately, to be rare in early intervention outcome studies in ASD. Thus, I wondered whether you are excluding too many studies

by selecting only RCTs and that perhaps by including studies that are not RCTs but have a comparison/ control group and then rating them all on quality (where clearly RCTs will receive higher scores than non-RCTs) might be more informative and inclusive of a larger body of available research.

Since the number of the RCTs of early interventions for children with ASD has been increasing recently, and we think that we will have enough RCTs to analyze selected outcomes for meta-analysis in this study (Around 20 RCTs will be enough to analyze and discuss appropriate outcomes in meta-analysis). We would like to avoid using non-RCTs for the analyses since this would reduce the evidence level of our conclusions.

Types of participants – the exact age range of participants and the exact diagnosis (i.e. autism, ASD, Asperger's PDD) need to be stated in this section and not later on, as the reader keeps wondering about these characteristics.

We changed description of the types of participants as below.

Participants comprise preschool children aged 0 to 6 with a diagnosis of ASD as below.
Diagnostic and statistical Manual of Mental Disorders-Ⅳ-Text Revision (DSM-Ⅳ-TR)
・Autistic disorder
・Asperger disorder
・Pervasive developmental disorder not otherwise specified (PDD-NOS)
International Classification of Diseases-10 (ICD-10)
・Childhood autism
・Asperger syndrome, atypical autism
・Other pervasive developmental disorders
・Pervasive developmental disorders, unspecified.

Types of interventions – this section is, in my opinion, the most challenging one to characterize and define. You have organized interventions into three groups, but it is unclear on what basis such a structure has emerged, thus this needs to be theoretically explained and supported by evidence.

We mentioned the definition of the three models based on a reference as shown above.

In addition, a major issue is that of "overlap" or "eclectic" approaches, which I am sure you are aware can often be the "norm" in ASD interventions rather than the exception.

ABA-based interventions are also multimodal, they also target a range of aspects of children's development and they also have a developmental focus, so what is of paramount importance is to clearly define and explain how you will group the interventions and how you will deal with comprehensive "eclectic" approaches. The reader needs to be clear how and why you organize the different interventions in the proposed categories.

We appreciate the Reviewer's point here. In any classification of intervention type there will be overlap situations. In our study, interventions which have elements that cross boundaries will be identified and this will be taken into account in the description and discussion phases of the study.

Types of outcome measures- primary measures need to be defined more clearly and I think it would be helpful to include examples of tools/ measures you will accept as measuring primary outcomes.

We added the examples of the tools/measures for the outcomes.

In more detail,

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in Diagnostic and Statistical Manual of Mental Disorders-IV-TR [16] and the definitional symptoms of the disorder and key indicators of psychopathology (e.g. the autism Diagnostic Observation Schedule-Generic (Lord et al., 2000) will be used for these outcomes.).

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are IQ and cognitive development (e.g. the Wechsler Preschool and Primary Scale of Intelligence third edition (Wechsler, 2002) will be used for these outcomes.).

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples (along with appropriate measures) are: measures of parent-child interaction (the Dyadic

Communication Measure for Autism; Aldred et al 2004), adaptive behavior (the Vineland Adaptive Behavior Scale; Sparrow et al., 2006), joint attention (the Early Social Communication Scales; Mundy et al., 2003), imitation ability (the Imitation Battery; Rogers et al, 2003), symbolic play (the Communication and Symbolic Behavior Scales Developmental Profile; Wetherby et al., 2002), receptive language (the MacArthur-Bates Communicative Development Inventory: Words and Gestures; Fenson et al., 2006), expressive language (the MacArthur-Bates Communicative Development Inventory; Fenson et al., 2006).

For example, it is not clear to me how qualitative impairments in social interaction and communication (primary outcome) may be that different to social communication in an interactive setting (intermediate outcome) and how you can clearly and unambiguously separate these (unless you do this by measure, in which case this section needs to be strengthened by including example measures). Adaptive behavior should also be clearly included (presumably in secondary outcome or primary outcome if you decide to measure socialization or communication subscales as primary).

We agree with your comment, and we deleted the outcomes, "social communication in an interactive setting". In addition, according to your suggestion, we added the outcome, "adaptive behaviour".

Searches - The words "treatment" and "therapy" were not included in your proposed search.

We added those terms to our proposed search. We changed the term "behavior therapy" to "behavior".

Data collection and analysis – Inclusion criteria 5 is most likely going to result in inclusion of a very small number of studies in your proposed meta-analysis, if any. Ethically, most studies cannot withhold early intervention from the control/ comparison groups, thus it is unlikely that you will find a study with a control group of children who did NOT receive early intervention for autism. Most RCTs with a waitlist control will be studies evaluating effectiveness of short-term, time-limited interventions, not comprehensive, long-term multimodal interventions such as the ones you propose to evaluate. Thus, I think it may be worthwhile reconsidering this criterion.

We deleted this criterion.

Also, in exclusion criteria 6 you mention "cognitive/behavioural" intervention. I am unclear why you included CBT ("cognitive") here for pre-school children.

It does not mean CBT but "cognitive intervention (e.g. targeted for enhancing joint attention) or behavioural intervention".

Exclusion criterion 3 also needs to be defined carefully as stating that "study did not report adequately" can be open to selection bias. What are the important information that you need to have?

Since exclusion criterion 3 is included in exclusion criteria 9 (Studies judged to be in high risk of bias according to the Cochrane Collaboration tool for assessing risk of bias), we omitted exclusion criteria 3.

Exclusion criteria 5 will also be problematic – most families of most children in most trials try a number of different interventions whether they are in the experimental or control group over and above the comprehensive intervention that is being evaluated and we know the percentages of families of children with ASD trying alternative medicine at some point are very high. If you exclude all these studies/ families, then it is likely your sample size of studies may be small and possibly not representative of interventions for pre-school children with ASD. You may want to consider these issues and revise the criteria.

We meant this not exclusion for the studies in which the participants used alternative medicine, but exclusion for the studies whose main targets were alternative medicine. Most of the alternative and complementary medicine in autism has not been established their effectiveness evidence (Akins et al., 2010). We changed exclusion criterion 5 as below.

Alternative or complementary medicine was used as the main intervention of the study.

In addition, we changed exclusion criteria, "The control group received some early intervention for children with autism" to "The control group received some specific early intervention for children with autism and the study compared two interventions' effectiveness."

Measures of treatment effect – Could you provide a reference for the statistical

analyses/ methods you are proposing for the readers (i.e. for random effects model using a standardized mean difference) as they are novel in this field?

We added a reference and revised this part as below.

Our review aims to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method in a random effect model (Higgins et al., 2008). We will compare the types of intervention model effectiveness for each outcome using a standardized mean difference.

Assessment of heterogeneity – if the meta-analysis includes such a small number of studies, I would argue that it would be more appropriate to revise the exclusion and inclusion criteria rather than set the p value to 0.10. Please see my comments above regarding some of the exclusion and inclusion criteria that I think will potentially be problematic and result in a very high exclusion of good quality published studies in the field. Please provide references for Chi2 test of consistently of results.

We added the references for random effects model using a standardized mean differences and Chi2 test of consistently of results as below. Since we will use random effect, not fixed effect, we will be able to synthesize data with heterogeneous. Thus, we delete the description about the p-value of Chi2 analyses.

Consistency of results will be assessed visually and by chi-square tests (Deeks et al., 2001). In addition, since chi-square can have low power when only few studies or studies of a small sample size are available, we will use the I^2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis (Higgins 2008).

The same point goes for subgroup analyses, you need to have enough studies to be able to carry out these potentially very informative analyses.

Revised inclusion and exclusion criteria will extract enough studies to carry out the subgroup analyses. There is a trade off between quality and number here. Since we will use random effect models, we will be able to synthesize the effect sizes even if the sample size is small.

P. 11 (measures of treatment effect) and p. 13 (data synthesis) are repetitive and exactly the same sentences are used in some parts.

We revised the section “measures of treatment effect” as below.

Measures of treatment effect

Continuous data

Continuous data will be analysed on the basis that the means and standard deviations are available and that there is no clear evidence of skew in the distribution.

Given the many challenges in trying to synthesize such complex literature, I would suggest that you consider including a section on "anticipated challenges and proposed course of action" so that the many difficulties discussed above can be openly and systematically addressed. One challenge I think is worth discussing in a little more detail includes how you will compare between findings from different studies with different time points (i.e. outcomes reported after 3, 6, 12, 24 months etc).

We mentioned the heterogeneity data as one of the challenges of this study in the discussion. Regarding the differences of the interventions' duration, we think it one of the variables which this kind of synthesizing analyses must contain. Some interventions with short durations will be included in this study. We will think about the durations of the interventions in the systematic review. We added that in the discussion.

In more detail:

Anticipated challenges in synthesize the literature exist. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We do not assume that each study is estimating exactly the same quantity. Thus, we will use random effect models for the analyses (Higgins et al., 2008). In addition, the durations of the interventions will be different among the studies included in this study. We will synthesize the data regardless of the durations of the interventions, and will discuss the diversity of the durations in our paper.

Finally, you mention "parent-mediated" vs "child-mediated" intervention delivery – I think it is important to define and clarify what you mean as most comprehensive interventions target the child but also most emphasize training the parents and parents working as co-therapists.

We added the definitions of "parent-mediated" and "child-mediated" as below.

·Parent-mediated (directing parents to train their children, not training the children directly) vs. child-mediated (training the children directly) intervention delivery.

Responses to Dr. Sigmund Eldevik's comments:

I think the study is set up appropriately. However, with the suggested inclsuion criteria my guess you would not be able to find an adequate number of studies to include. I think such a study should be done, but I think you need to adjust inclusion criteria so that a meaningful number of studies could be included.

We revised our inclusion and exclusion criteria. We will be able to perform the analyses even if there are only several studies included into each model. Our revised criteria will compare each model on important outcome measures (or areas of measurement) that are common across studies.

All correspondence should be sent to
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We are looking forward to your replies.

Sincerely yours,
Yoshiyuki Tachibana

A systematic review with meta-analysis of comprehensive interventions for pre-school children with autism spectrum disorder: study protocol

~~A systematic review with meta-analysis of different models of intervention for pre-school autism: study protocol~~

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ABSTRACT

~~Aim~~**Introduction:** The aims of our study are to: i) conduct a systematic review of the intervention literature in preschool autism spectrum disorder (ASD), including type of intervention that is tested and classification of outcome measures used; ii) to undertake a meta-analysis of the studies, allowing for the first time the comparison of different approaches to intervention using comparative outcomes.

~~**Background:**~~ There are a number of alternative modalities of intervention for preschool ASD in use with different theoretical background and orientation, each of which tend to use different trial designs and outcome measures~~; and there has been no comparative review to date across intervention modality in order to inform clinical decisions~~. There is at this time an urgent need for comprehensive systematic review and meta-analyses of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for pre-school interventions in the disorder.

~~**Design and methods**~~**Methods and analysis:** We will perform a systematic review of RCTs for preschool children with ASD aged 0 to 6, along with a meta-analysis of qualifying studies across intervention modality. We will classify the interventions for preschool ASD under three models; behaviour, multi-modal developmental, and communication-focused. Firstly, we will perform a systematic review. Then, we will conduct a meta-analysis by comparing the three models with various outcomes using an inverse variance method in a random effect model. We will synthesize each outcome of the studies for the three models using standardized mean differences.

~~**Discussion**~~**Dissemination and ethics:** This study will identify each intervention's strengths and weaknesses. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. ~~This study may also~~

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~~reveal what points are lacking among the current intervention programmes for children with ASD.~~ We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

Trial registration:

http://www.crd.york.ac.uk/prospero/register_new_review.asp?RecordID=1349&UserID=230 (Registration No. CRD42011001349)

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INTRODUCTION

Recent epidemiological studies estimate a prevalence of 1:100 for autism spectrum disorder (ASD) [1], which is a surprising increase over rates reported in the past [2]. There has been increasing interest in developing effective interventions for young children with ASD, since the evidence suggests that early intervention programmes are indeed beneficial for children with ASD, often improving developmental functioning and decreasing maladaptive behaviours and symptom severity [3], and also can improve outcomes in later years for most individuals [4].

An increasing volume of published trials of psychosocial intervention programmes for preschool ASD have been seen in recent years. These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism; iii) multimodal interventions targeted across areas of autistic children's development. In addition, an increasing number of these studies have followed CONSORT guidelines [5], and some meta-analyses and systematic reviews about intervention programmes for preschool children have been published; e.g. [6-8]. These meta-analyses and systematic reviews focused exclusively on one or other of these groups of intervention styles; there has been no systematic review or meta-analysis of studies comparing results from different types of intervention approach from the viewpoint of the three models. For clinicians and commissioners this poses a difficulty in making general choices in a field containing often strong and partisan claims of effect from different traditions of intervention. Related to this, there has been great variation in endpoint measures used in these reported studies, making comparison of effects difficult. Specifically, there has been variation in whether endpoints have been framed in terms of autism symptom outcomes, non autism-specific outcomes, or intermediate developmental endpoints; and these latter two have often

been reported as if they were surrogate endpoints for autism-specific symptoms or disorder. We think that these considerations indicate the need for a more comprehensive review of intervention studies for preschool ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder. In this study, we will investigate it by comparing three major types of interventions with various outcomes.

We will undertake a systematic review and a meta-analysis of RCTs for preschool children with ASD. Recently many RCTs for children with ASD have been emerged as sufficient as to perform meta-analyses. RCT methodology has been identified as the gold standard in efficacy research [9]. In addition, meta-analyses of RCTs is the top hierarchy of evidence based medicine [10]. Thus, the findings of this study will be very strong evidence about interventions for children with ASD. Howlin et al. are asserting that there are three main strands of early interventions for children with ASD): programs with a particular emphasis on the use of behavioural principle to improve learning and behaviour; those that have a specific focus on communication; and those in which developmental/educational strategies have been employed [11]. In this study, we named those strands as behavioural, communication-focused, and multimodal developmental interventions, respectively. ~~We classify the interventions for preschool children with ASD under the three models; i.e. behaviour model, developmental model, and communication focused model.~~ Understanding the mechanisms that underlie this attenuation of treatment effects and how these can be overcome is one current challenge [12]. This study may reveal each type of the intervention's strong and weak points~~This study will reveal which type of interventions is the most effective~~ to various kinds of treatment factors respectively. Its findings will guide us to develop new types of interventions to overcome the attenuation of treatment effects in the core symptoms of

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autism. It will contribute to the appropriate choices of the interventions for children with ASD for their families, clinicians, and the policymakers.

The objective of our study is to: i) conduct a systematic review of all the preschool intervention literature in ASD, including the type of intervention that is being tested and classification of outcome measures used; ii) to undertake a meta-analysis of methodologically adequate studies using the Cochrane tool, which will allow for the first time comparison of different approaches to intervention on comparative outcome measures.

METHODS

Types of studies

We will include randomized controlled trials and subject these to a rating on quality criteria.

Types of participants

Participants comprise preschool children aged 0 to 6 with a diagnosis of ASD as below.

Diagnostic and statistical Manual of Mental Disorders-Ⅳ-Text Revision (DSM-Ⅳ-TR) [13]

・Autistic disorder

・Asperger disorder

・Pervasive developmental disorder not otherwise specified (PDD-NOS)

International Classification of Diseases-10 (ICD-10) [14]

・Childhood autism

・Asperger syndrome, atypical autism

・Other pervasive developmental disorders

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- Pervasive developmental disorders, unspecified.

~~Participants comprise preschool children with a diagnosis of autism spectrum disorder (ASD) aged 0 to 6.~~

Types of interventions

We classify interventions for preschool ASD in three groups; i) behavioural interventions – based essentially on learning theory and on applied behaviour analysis; ii) communication-focused interventions, targeting social communication impairment, as the core symptom of autism; iii) multimodal developmental interventions targeting a range of aspects of children's development.

Types of outcome measures

A feature of this review is that we will systematically classify the various outcome measures used within recent intervention trials into the following categories:

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in DSM-IV-TR and the definitional symptoms of the disorder and key indicators of psychopathology (e.g. the autism Diagnostic Observation Schedule-Generic [15] will be used for these outcomes.).

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are IQ

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and cognitive development (e.g. the Wechsler Preschool and Primary Scale of Intelligence third edition [16] will be used for these outcomes.).

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples (along with appropriate measures) are: measures of adaptive behavior (the Vineland Adaptive Behavior Scale [17]), joint attention (the Early Social Communication Scales [18]), imitation ability (the Imitation Battery [19]), symbolic play (the Communication and Symbolic Behavior Scales Developmental Profile [20]) , parent-child interaction (the Dyadic Communication Measure for Autism [21]), receptive language (the MacArthur-Bates Communicative Development Inventory (MCDI [22])), expressive language (MCDI [22]).

~~Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples are: measures of joint attention, parent child interaction, imitation ability, symbolic play, social communication in an interactive setting, receptive language, expressive language.~~

Electronic searches

We will do a systematic review of the published work according to the PRISMA statement [23]. Relevant studies will be identified by searching the following data sources: PsycINFO (from 1956 to January, 2011), Medline via Ovid (from 1950 to January, 2011), ERIC (from 1950 to January, 2011) and the Cochrane database.

We will use the following search terms to search all trials registers and databases: “autism” , “autism spectrum disorder”, “ASD”, “high function autism”, “high function ASD”, “Asperger syndrome”, “pervasive developmental disorder”, “PDDNOS”,

"intervention", "treatment", "therapy", "communication", "interpersonal", "speech", "interaction", "synchrony", "relationship", "language", "social" and "development", "behavior therapy", "intensive behavioral intervention". Their search will be limited by age group from 0 to 6 years old and "randomized controlled trial." This search strategy has been peer-reviewed by a librarian of University of Manchester.

Validity assessment

Two of the authors, Y.T., Y.H. independently will review abstracts of potentially the relevant studies. This will be followed by a consensus discussion with J.G. The quality of the RCTs will be coded independently by Y.T. and Y.H. and disagreement will be resolved by consensus discussions.

Searching other resources

Reference lists from identified trials and review articles will be manually scanned to identify any other relevant studies. The clinicalTials.gov and the Cochrane Library website will be also searched for randomized trials that were registered as completed but not yet published.

Data collection and analysis

Selection of studies

Inclusion:

1. Participants comprise preschool children with a diagnosis of ASD or pervasive developmental disorder (PDD).

2. Randomized controlled trials

3. Interventions delivered to the parents/guardians and/or directly to the child, by special educators, teachers, speech pathologists, psychologists, or other allied health professional students will be included.

4. Studies carried out while the children were at a preschool age between 0 and 6 years.

~~5. The control group will be those who did not received early intervention for autism.~~

~~6. Studies judged to be in low risk of bias according to the Cochrane Collaboration tool for assessing risk of bias~~

Exclusion:

1. The study was not primary research on preschool autism.

2. The study did not assess a cognitive/behavioural intervention for preschool autism.

~~3. The study did not report adequately on any measurable data for health related outcomes relevant to the review.~~

34. The study design was not a randomized controlled trial.

45. ~~The intervention used alternative medicine.~~ Alternative or complementary medicine was used as the main intervention of the study.

56. The intervention was pharmacological one.

67. The intervention was not classified into behavioural, multimodal developmental or communication-focused model.

78. The control group received ~~a~~ a specific early intervention programme for children with autism which was not a usual treatment provided by their local services.~~some early intervention for children with autism~~.

89. Studies judged to be in high risk of bias according to the Cochrane Collaboration tool for assessing risk of bias

All citations sourced from the search strategy will be transferred to EndNote, a reference management database software. Initial screening of titles and abstracts by an

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experienced research fellow (YT) will eliminate all those citations obviously irrelevant to the topic, for example, prevalence studies, studies not relating to autism spectrum disorders, single case studies. Thereafter, two review authors (YT and YH) will assess and select studies for inclusion from the group of superficially relevant studies. In the event of a disagreement, resolution will be reached in discussion with the third author (JG), if necessary following inspection of the full paper.

Data extraction and management

YT and YH will independently extract data from selected trials using a specially designed data extraction form. Extracted data will consist of methods (dose and frequency of intervention); diagnostic description of participants, and type of intervention, including target, intensity, duration and method of application (parent-mediated, therapist, school-based etc.). Data will be extracted independently by two review authors (YT and YH) and disagreements will be resolved by negotiation with a third author (JG).

Assessment of risk of bias in the studies

Risk of bias will be assessed by two independent review authors (YT and YH) and disagreements will be resolved by negotiation with a third review author (JG). We will use the Cochrane Collaboration tool for assessing risk of bias in these areas [24]. The assessed risk of bias in studies will include in the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other sources of bias. The process will involve recording the appropriate information for each study (for example describing the method used to conceal allocation in detail) and evaluating whether there is risk of bias in that area (for

example, was allocation adequately concealed). We will allocate studies to the three categories according to our judgment of each area or potential risk of bias: A. Low risk of bias; B. Moderate (or unclear) risk of bias; C. High risk of bias. Whether the studies should be included for the analyses or not will be judged individually based on the results of the risk of bias assessments.

Measures of treatment effect

Continuous data

Continuous data will be analysed on the basis that the means and standard deviations are available and that there is no clear evidence of skew in the distribution.

~~**Measures of treatment effect**~~

~~The categories of outcome measure differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims for the first time to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses, comparing type of intervention model effectiveness for each outcome using a standardized mean difference. This is a novel approach for this field.~~

Dealing with missing data

Missing data will be assessed for each individual study. Where a loss of significant quantities of participant data is reported such that the review authors agree that the conclusions of the study are compromised, trial authors will be contacted. If no reply is

forthcoming or full data are not made available, these studies will not be included in the final analysis. For included studies reporting drop-out, we will report the number of participants included in the final analysis as a proportion of those participants who began the intervention. Reasons for missing data will be reported. The extent to which the results of the review could be altered by the missing data will be assessed and discussed. If summary data are missing, trial authors will be contacted. If no reply is forthcoming or the required summaries are not made available, the authors will include the study in the review and assess and discuss the extent to which its absence from meta-analysis affects the review results.

Assessment of heterogeneity

Consistency of results will be assessed visually and by chi-square tests [25]. In addition, since chi-square can have low power when only few studies or studies of a small sample size are available [26], we will use the I^2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis [27].

~~Consistency of results will be assessed visually and by a Chi2 test. If the meta-analysis includes only a small number of studies, or where studies have small sample sizes, a P value of 0.10 will be applied for statistical significance. In addition, since Chi2 can have low power when only few studies or studies of a small sample size are available, we will use the I2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis (Higgins 2008).~~

Assessment of reporting biases

If sufficient studies are found, funnel plots will be drawn to investigate any relationship between effect size and sample size. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. If a relationship is identified, clinical diversity of the studies will be further examined as a possible explanation. Every attempt will be made to obtain unpublished data and data from conference proceedings.

Data synthesis

Data synthesis will be performed using Review Manager version 5.1 (Cochrane Collaboration software). We will assess continuous and binary data. Assuming that two or more studies that are suitable for inclusion are found, and that the studies are considered to be homogenous, a meta-analysis will be performed on the results. The categories of outcome measure mentioned above differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method in a random effect model[27]. ~~The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses [27], since we do not assume that each study is estimating exactly the same quantity.~~ We will compare the types of intervention model effectiveness for each outcome using a standardized mean difference.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses and meta-regression and where no significant heterogeneity of effect sizes is found, these will be pooled to calculate a final effect size. While these analyses may enable us to hypothesize as to possible causes of differences between studies' findings, some heterogeneity is likely to remain, and any statistical analysis will be accompanied by a narrative synthesis.

Subgroup analysis will be undertaken if clinically different interventions are identified, or there are clinically relevant differences between participant groups. Anticipated clinically relevant differences are:

1. intervention delivery type (e.g. therapist, parent-mediated, school-based) and length

2. intervention target skill (e.g. Theory of Mind as a whole, joint attention, emotion recognition, false belief understanding)

3. participant age (e.g. preschool, young children, adolescents, adults), IQ (low versus normal or high), specific diagnosis and verbal ability.

Relevant subgroup analyses will also include:

·Severity of autism at baseline. This is a crucial element in evaluating autism studies.

·Social economic status ~~SES~~ and other demographic variables. Sampling bias and external validity of studies is an important consideration.

·Age of child

·Type of intervention (our 3 groups as above)

·Parent-mediated (directing parents to train their children, not training the children directly) vs. child-mediated (training the children directly) intervention delivery~~. A key distinguishing point between different studies in the area.~~

·Cognitive ability at baseline

Sensitivity analysis

Sensitivity analysis will be conducted to assess the impact of study quality on the results of the meta-analyses. For example, we will test to see if studies with high rates of loss to follow up or inadequate blinding are more likely to show positive outcomes and also to assess the impact of imputing missing data.

DISCUSSION

We believe that the findings of this systematic review and meta-analysis will have important implications for both clinical practice and research. Meta-analysis of ~~randomized controlled trial~~RCTs of the interventions for preschool children with ASD will provide the most reliable basis for the decisions of early interventions for them. Analyses as to the three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD. This study will provide information about which kind of intervention has strength points and weak points, and what are those strength points and weak points are. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. ~~This study may also reveal what points are lacking among the current intervention programmes for children with ASD.~~ We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits. Anticipated challenges in synthesize the literature exist. The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We do not assume that each study is estimating exactly the same quantity. Thus, we will use random effect models for the analyses [27]. In addition, the durations of the interventions will be different among the studies included in this study. We will synthesize the data regardless of the durations of the interventions, and will discuss the diversity of the durations in our paper.

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Authors' contribution YT and JG contributed to draft the protocol and develop a search strategy. YT also drafted this manuscript. RE contributed to provide statistical advice for the design and the analysis. All authors read and approved the final manuscript.

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Competing interests None.

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A systematic review with meta-analysis of comprehensive interventions for preschool children with autism spectrum disorder: study protocol

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A systematic review with meta-analysis of comprehensive interventions for pre-school children with autism spectrum disorder (ASD): study protocol

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ABSTRACT

Introduction: The aims of our study are to: i) conduct a systematic review of the intervention literature in preschool children with autism spectrum disorder (ASD), including types of interventions that are tested and the classification of outcome measures used; ii) to undertake a meta-analysis of the studies, allowing for the first time the comparison of different approaches to intervention using comparative outcomes. There are a number of alternative modalities of intervention for preschool children with ASD in use with different theoretical background and orientation, each of which tend to use different trial designs and outcome measures. There is at this time an urgent need for comprehensive systematic review and meta-analyses of intervention studies for preschool children with ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder.

Methods and analysis: We will perform a systematic review of RCTs for preschool children with ASD aged 0 to 6, along with a meta-analysis of qualifying studies across intervention modality. We will classify the interventions for preschool children with ASD under three models; behaviour, multi-modal developmental, and communication-focused. Firstly, we will perform a systematic review. Then, we will conduct a meta-analysis by comparing the three models with various outcomes using an inverse variance method in a random effect model. We will synthesise each outcome of the studies for the three models using standardised mean differences.

Dissemination and ethics: This study will identify each intervention's strengths and weaknesses. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

Trial registration:

http://www.crd.york.ac.uk/prospero/register_new_review.asp?RecordID=1349&UserID=230 (Registration No. CRD42011001349)

INTRODUCTION

Recent epidemiological studies estimate a prevalence of 1:100 for autism spectrum disorder (ASD) [1], an increase over reported rates in the past [2]. There has been increasing interest in developing effective interventions for young children with ASD, since the evidence suggests that early intervention programmes are indeed beneficial for children with ASD, often improving developmental functioning and decreasing maladaptive behaviours and symptom severity [3], and also can improve outcomes in later years for many individuals [4].

An increasing volume of published trials of psychosocial intervention programmes for preschool children with ASD have been seen in recent years. These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA) (e.g. [5]); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism (e.g. [6]); iii) multimodal interventions targeted across areas of autistic children's development (e.g. [7]). In addition, an increasing number of these studies have followed CONSORT guidelines [8], and some meta-analyses and systematic reviews about intervention programmes for preschool children with ASD have been published; e.g. [9-11]. These meta-analyses and systematic reviews focused exclusively on one or the others of these groups of intervention styles; there has been no systematic review or meta-analysis of studies comparing results from different types of intervention approach from the viewpoint of the three models. For clinicians and commissioners this poses a difficulty in making general choices in a field containing often strong and partisan claims of effect from different traditions of intervention. Related to this, there has been great variation in endpoint measures used in these reported studies, making comparison of effects between studies difficult. Specifically, there has been variation in whether endpoints have been framed in terms of specific autism symptom outcomes, non autism-specific

outcomes that are not specific to autism (such as for instance IQ), or 'intermediate' endpoints relating to aspects of development that may have some relationship to later autism symptoms – examples would be changes in joint attention or parent-child interaction. These latter two kinds of outcome are often reported, without necessarily strong justification, as if they were the equivalent of change in autism symptoms (i.e. as 'surrogate' endpoints); and this can cause real confusion. We think that these considerations indicate the need for a more comprehensive review of intervention studies for preschool children with ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder. In this study, we will investigate it by comparing three major types of interventions with various outcomes.

We will undertake a systematic review and a meta-analysis of RCTs for preschool children with ASD. Recently, many RCTs for children with ASD have emerged sufficient enough to perform meta-analyses. RCT methodology has been identified as the gold standard in efficacy research [12]. In addition, meta-analyses of RCTs is at the top of the evidence based medicine hierarchy [13]. Thus, the findings of this study will provide strong evidence about interventions for children with ASD. Howlin et al. are asserting that there are three main strands of early interventions for children with ASD): programmes with a particular emphasis on the use of behavioural principle to improve learning and behaviour; those that have a specific focus on communication; and those in which developmental/educational strategies have been employed [14]. In this study, we named those strands as behavioural, communication-focused, and multimodal developmental interventions, respectively. Understanding the mechanisms that underlie this attenuation of treatment effects and how these can be overcome is one current challenge [15]. This study may reveal each type of the intervention's strong and weak points to various kinds of treatment factors respectively. Its findings will guide us to

develop new types of interventions to overcome the attenuation of treatment effects in the core symptoms of autism. It will contribute to the appropriate choices of the interventions for children with ASD for their families, clinicians, and the policymakers.

The objective of our study is to: i) conduct a systematic review of all the preschool intervention literature in ASD, including the type of intervention that is being tested and classification of outcome measures used; ii) to undertake a meta-analysis of methodologically adequate studies using the Cochrane tool, which will allow for the first time comparison of different approaches to intervention on comparative outcome measures.

METHODS

Types of studies

We will include randomised controlled trials and subject these to a rating on the Cochrane Collaboration tool for assessing risk of bias.

Types of participants

Participants comprise preschool children aged 0 to 6 with a diagnosis of ASD as below.

Diagnostic and statistical Manual of Mental Disorders-Ⅳ-Text Revision (DSM-Ⅳ-TR) [16]

- Autistic disorder
- Asperger disorder
- Pervasive developmental disorder not otherwise specified (PDD-NOS)

International Classification of Diseases-10 (ICD-10) [17]

- Childhood autism
- Asperger syndrome, atypical autism

- Other pervasive developmental disorders
- Pervasive developmental disorders, unspecified.

Types of interventions

We classify interventions for preschool children with ASD in three groups; i) behavioural interventions – based essentially on learning theory and on applied behaviour analysis; ii) communication-focused interventions, targeting social communication impairment, as the core symptom of autism; iii) multimodal developmental interventions targeting a range of aspects of children's development.

Types of outcome measures

A feature of this review is that we will systematically classify the various outcome measures used within recent intervention trials into the following categories:

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in DSM-Ⅳ-TR and the definitional symptoms of the disorder and key indicators of psychopathology (e.g. the autism Diagnostic Observation Schedule-Generic [18] will be used for these outcomes.).

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are adaptive behaviour (e.g. the Vineland Adaptive Behaviour Scale [19] will be used for this

outcome), and IQ and cognitive development (e.g. the Wechsler Preschool and Primary Scale of Intelligence third edition [20] will be used for these outcomes.).

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples (along with appropriate measures) are: measures of joint attention (the Early Social Communication Scales [21]), imitation ability (the Imitation Battery [22]), symbolic play (the Communication and Symbolic Behaviour Scales Developmental Profile [23]), parent-child interaction (the Dyadic Communication Measure for Autism [24]), receptive language (the MacArthur-Bates Communicative Development Inventory (MCDI [25])), expressive language (MCDI [25]).

Electronic searches

We will do a systematic review of the published work according to the PRISMA statement [26]. Relevant studies will be identified by searching the following data sources: PsycINFO (from 1956 to January, 2011), Medline via Ovid (from 1950 to January, 2011), ERIC (from 1950 to January, 2011) and the Cochrane database.

We will use the following search terms to search all trials registers and databases: “autism” , “autism spectrum disorder”, “ASD”, “high function autism”, “high function ASD”, “Asperger syndrome”, “pervasive developmental disorder”, “PDDNOS”, “intervention”, “treatment”, “therapy”, “communication”, “interpersonal”, “speech”, “interaction”, “synchrony”, “relationship”, “language”, “social”, “development”, “behavior”, “intensive behavioral intervention”, “trial”, and “outcome”. Their search will be limited by age group from 0 to 6 years old and “randomized controlled trial.” This search strategy has been peer-reviewed by a librarian of University of Manchester.

Validity assessment

Two of the authors, Y.T., Y.H. will independently review the abstracts of the potentially relevant studies. This will be followed by a consensus discussion with J.G. The quality of the RCTs will be coded independently by Y.T. and Y.H. and disagreements will be resolved by consensus discussions.

Searching other resources

Reference lists from identified trials and review articles will be manually scanned to identify any other relevant studies. The clinicalTials.gov and the Cochrane Library website will be also searched for randomised trials that were registered as completed but not yet published.

Data collection and analysis

Selection of studies

Inclusion:

1. Participants comprise preschool children with a diagnosis of ASD or pervasive developmental disorder (PDD).

2. Randomised controlled trials

3. Interventions delivered to the parents/guardians and/or directly to the child, by special educators, teachers, speech pathologists, psychologists, or other allied health professional students will be included.

4. Studies carried out while the children were at a preschool age between 0 and 6 years.

Exclusion:

1. The study was not primary research on preschool children with ASD.

2. The study did not assess a cognitive/behavioural intervention for preschool children with ASD.

3. The study design was not a randomised controlled trial.

4. Alternative or complementary medicine was used as the main intervention of the study.

5. The intervention was a pharmacological one.

6. The intervention was not classified into behavioural, multimodal developmental or communication-focused model.

7. The control group received a specific early intervention programme for children with autism which was not a usual treatment provided by their local services.

8. The study was judged to be in high risk of bias by the Cochrane Collaboration tool for assessing risk of bias.

All citations sourced from the search strategy will be transferred to EndNote, a reference management database software. Initial screening of titles and abstracts by an experienced research fellow (YT) will eliminate all those citations obviously irrelevant to the topic, for example, prevalence studies, studies not relating to autism spectrum disorders, single case studies. Thereafter, two review authors (YT and YH) will assess and select studies for inclusion from the group of superficially relevant studies. In the event of a disagreement, resolution will be reached in discussion with the third author (JG), if necessary following inspection of the full paper.

Data extraction and management

YT and YH will independently extract data from selected trials using a specially designed data extraction form. Extracted data will consist of methods (dose and frequency of intervention); diagnostic description of participants, and type of

intervention, including target, intensity, duration and method of application (parent-mediated, therapist, school-based etc.). Data will be extracted independently by two review authors (YT and YH) and disagreements will be resolved by negotiation with a third author (JG).

Assessment of risk of bias in the studies

Risk of bias will be assessed by two independent review authors (YT and YH) and disagreements will be resolved by negotiation with a third review author (JG). We will use the Cochrane Collaboration tool for assessing risk of bias in these areas [27]. The assessed risk of bias in studies will include in the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other sources of bias. The process will involve recording the appropriate information for each study (for example describing the method used to conceal allocation in detail) and evaluating whether there is risk of bias in that area (for example, was allocation adequately concealed). We will allocate studies to the three categories according to our judgment of each area or potential risk of bias: A. Low risk of bias; B. Moderate (or unclear) risk of bias; C. High risk of bias. Whether the studies should be included for the analyses or not will be judged individually based on the results of the risk of bias assessments.

Measures of treatment effect

Continuous data

Continuous data will be analysed on the basis that the means and standard deviations are available and that there is no clear evidence of skew in the distribution.

Dealing with missing data

Missing data will be assessed for each individual study. Where a loss of significant quantities of participant data is reported such that the review authors agree that the conclusions of the study are compromised, trial authors will be contacted. If no reply is forthcoming or full data are not made available, these studies will not be included in the final analysis. For included studies reporting drop-out, we will report the number of participants included in the final analysis as a proportion of those participants who began the intervention. Reasons for missing data will be reported. The extent to which the results of the review could be altered by the missing data will be assessed and discussed. If summary data are missing, trial authors will be contacted. If no reply is forthcoming or the required summaries are not made available, the authors will include the study in the review and assess and discuss the extent to which its absence from meta-analysis affects the review results.

Assessment of heterogeneity

Consistency of results will be assessed visually and by chi-square tests [28]. In addition, since chi-square can have low power when only few studies or studies of a small sample size are available [29], we will use the I^2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis [30].

Assessment of reporting biases

If sufficient studies are found, funnel plots will be drawn to investigate any relationship between effect size and sample size. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. If a

relationship is identified, clinical diversity of the studies will be further examined as a possible explanation. Every attempt will be made to obtain unpublished data and data from conference proceedings.

Data synthesis

Data synthesis will be performed using Review Manager version 5.1 (Cochrane Collaboration software). We will assess continuous and binary data. Assuming that two or more studies that are suitable for inclusion are found, and that the studies are considered to be homogenous, a meta-analysis will be performed on the results. The categories of outcome measure mentioned above differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims to make comparison across these different types of intervention study, thus we will standardise and synthesise the various categories of outcome measure using an inverse variance method in a random effect model[30]. We will compare the types of intervention model effectiveness for each outcome using a standardised mean difference.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses and meta-regression. These will be pooled to calculate a final effect size. While these analyses may enable us to hypothesise as to possible causes of differences between studies' findings, some heterogeneity is likely to remain, and any statistical analysis will be accompanied by a narrative synthesis.

Subgroup analysis will be undertaken if clinically different interventions are identified, or there are clinically relevant differences between participant groups. Anticipated clinically relevant differences are:

1. intervention delivery type (e.g. therapist, parent-mediated, school-based) and length

2. intervention target skill (e.g. Theory of Mind as a whole, joint attention, emotion recognition, false belief understanding)

3. participant age (e.g. preschool, young children), IQ (low versus normal or high), specific diagnosis and verbal ability.

Relevant subgroup analyses will also include:

·Severity of autism at baseline

·Social economic status and other demographic variables

·Age of child

·Type of intervention (our 3 groups as above)

·Parent-mediated (directing parents to train their children, not training the children directly) vs. child-mediated (training the children directly) intervention delivery

·Cognitive ability at baseline

Sensitivity analysis

Sensitivity analysis will be conducted to assess the impact of study quality on the results of the meta-analyses. For example, we will test to see if studies with high rates of loss to follow up or inadequate blinding are more likely to show positive outcomes and also to assess the impact of imputing missing data.

DISCUSSION

Meta-analysis of RCTs across types of intervention for preschool children with ASD is an important step in providing a reliable basis for implementation decisions. Since previous analyses have been essentially restricted to specific intervention types, and often with different outcome criteria, a study across three representative models:

behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD. This study will provide information about which kind of intervention has strong points and weak points, and what are those strong points and weak points are. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits. Anticipated challenges in synthesise the literature exist. The measures used for outcome are varied between studies and the standardised data will be heterogeneous. We do not assume that each study is estimating exactly the same quantity. Thus, we will use random effect models for the analyses [30]. In addition, the durations of the interventions will be different among the studies included in this study. We will synthesise the data regardless of the durations of the interventions, and will discuss the diversity of the durations in our paper.

Authors' contribution YT and JG contributed to draft the protocol and develop a search strategy. YT also drafted this manuscript. RE contributed to provide statistical advice for the design and the analysis. All authors read and approved the final manuscript.

Acknowledgement We thank Claire Hodkinson for the peer-reviewing of this study's search strategy.

Competing interests None.

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Systematic reviews in health care 2001:285-312.

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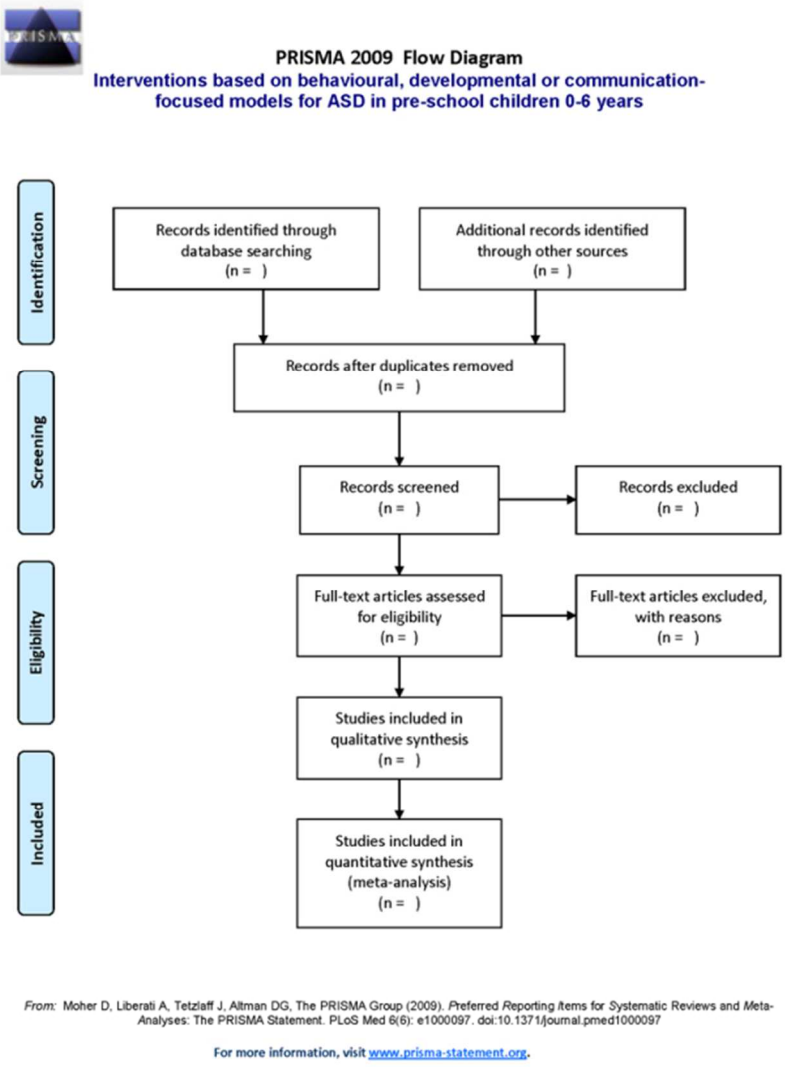

Caption: Figure 1
Legend: Flow diagram of this study

January 20th, 2012

The BMJ Open Editorial Office
Dear Editor,
RE: BMJ Open - Decision on Manuscript ID bmjopen-2011-000679.R1

Thank you very much for your editorial work on our manuscript entitled "A systematic review with meta-analysis of comprehensive interventions for preschool children with autism spectrum disorder: study protocol". We also very much appreciate Dr. Iliana Magiati's helpful suggestions. We took her comments into account in our revised manuscript.

Responses to Dr. Iliana Magiati's comments:

- Consider replacing the term "preschool autism spectrum disorder" with "preschool children with ASD" throughout the document in order to meet APA guidelines regarding best use of language to describe participants

The term "preschool autism spectrum disorder" has now been replaced with "preschool children with ASD" throughout the document.

- Despite the good standard of English language, I would still advice the authors to review their manuscript one more time for grammar and syntax.

Our manuscript has now been reviewed for grammar and syntax.

- Change "most" individuals in final line of first paragraph to "many" individuals – in fact, many outcome studies in adulthood show that many individuals remain very vulnerable and in need of services.

This has now been changed.

- Please consider including one or two references as examples of behavioral, social-communication and multimodal developmental interventions in the second paragraph of the introduction.

One reference for each model has now been included.

In more detail,

These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA) (e.g. [5]); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of

autism (e.g. [6]); iii) multimodal interventions targeted across areas of autistic children's development (e.g. [7]).

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5. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. American Journal on Mental Retardation 2000;105(4):269-85.

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7. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics 2010;125(1):e17.

- Can you clarify what you mean by "intermediate developmental endpoints" and "surrogate endpoints" (p.4, last line, p.5 first line)?

'Surrogate endpoint' is a well characterized term in the trials and intervention literature – essential an intermediate outcome that is a proximal equivalent to the endpoint change desired (for in change in immune status after vaccine) and can in some way 'stand for it'. The text now clarifies our meaning here in relation to the intermediate developmental endpoints reported in studies.

In more detail,

Specifically, there has been variation in whether endpoints have been framed in terms of specific autism symptom outcomes, non autism-specific outcomes that are not specific to autism (such as for instance IQ), or 'intermediate' endpoints relating to aspects of development that may have some relationship to later autism symptoms – examples would be changes in joint attention or parent-child interaction. These latter two kinds of outcome are often reported, without necessarily strong justification, as if they were the equivalent of change in autism symptoms (i.e. as 'surrogate' endpoints); and this can cause real confusion.

- Clarify the "quality criteria" ratings mentioned in Methods, Type of Studies section.

This part has now been corrected as below.

We will include randomized controlled trials and subject these to a rating on the Cochrane Collaboration tool for assessing risk of bias.

- I am not sure that "adaptive behavior functioning" as measured by the Vineland Adaptive Behaviour Scales constitutes an intermediate outcome – social and communication skills are primary areas of difficulty in ASD and I would think they are primary or secondary outcome.

We agree with the reviewer and "Adaptive behaviour functioning" has now been put into the secondary outcomes.

- Please consider including "trial" and "outcome" too in your search terms.

These have now been included in the search terms.

- The exclusion criteria need to be more clearly written with more attention to language/ grammar.

The exclusion criteria have now been corrected.

- With exclusion criterion 7 do you mean that you will exclude all studies who do not have a TAU comparison group? What if a study compares a behavioral with a developmental approach? Wouldn't the findings of such a study be directly relevant to the aims of your systematic review and meta-analysis?

We need to limit the studies to those using a TAU comparison group because of our statistical analyses. Following Cochrane Handbook for Systematic Reviews of Intervention, we are using an inverse variance method within a random effects model. This requires treatment of TAU arms in a standard way – excluding comparisons of two test treatments in which the baselines are not TAU.

- Please delete the age groups of adolescents and adults from your list in p. 13, point 3, as your study is only on pre-school children.

These have now been deleted.

- The first paragraph of the discussion needs to be written in a more "moderate" tone – i.e. "this study will provide the most reliable basis for decisions on early intervention". Clearly this depends on the quality of the study eventually so best to rephrase to "can provide a more reliable basis".

The first paragraph of the discussion has now been corrected according to these comments.

In more detail,

Meta-analysis of RCTs across types of intervention for preschool children with ASD is an important step in providing a reliable basis for implementation decisions. Since previous analyses have been essentially restricted to specific intervention types, and often with different outcome criteria, a study across three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD.

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We are looking forward to your replies.

Sincerely yours,
Yoshiyuki Tachibana

A systematic review with meta-analysis of comprehensive interventions for pre-school children with autism spectrum disorder (ASD): study protocol

~~A systematic review with meta-analysis of different models of intervention for pre-school autism: study protocol~~

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ABSTRACT

~~Aim~~**Introduction:** The aims of our study are to: i) conduct a systematic review of the intervention literature in preschool children with autism spectrum disorder (ASD), including types of interventions that ~~is~~ are tested and the classification of outcome measures used; ii) to undertake a meta-analysis of the studies, allowing for the first time the comparison of different approaches to intervention using comparative outcomes.

~~**Background:**~~ There are a number of alternative modalities of intervention for preschool children with ASD in use with different theoretical background and orientation, each of which tend to use different trial designs and outcome measures~~; and there has been no comparative review to date across intervention modality in order to inform clinical decisions~~. There is at this time an urgent need for comprehensive systematic review and meta-analyses of intervention studies for preschool children with ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for pre-school interventions in the disorder.

~~**Design and methods**~~**Methods and analysis:** We will perform a systematic review of RCTs for preschool children with ASD aged 0 to 6, along with a meta-analysis of qualifying studies across intervention modality. We will classify the interventions for preschool children with ASD under three models; behaviour, multi-modal developmental, and communication-focused. Firstly, we will perform a systematic review. Then, we will conduct a meta-analysis by comparing the three models with various outcomes using an inverse variance method in a random effect model. We will synthesis~~z~~e each outcome of the studies for the three models using ~~standardized~~ standardised mean differences.

~~**Discussion**~~**Dissemination and ethics:** This study will identify each intervention's strengths and weaknesses. This study may also suggest what kinds of elements future

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intervention programmes for children with ASD should have. ~~This study may also reveal what points are lacking among the current intervention programmes for children with ASD.~~ We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits.

Trial registration:

http://www.crd.york.ac.uk/prospero/register_new_review.asp?RecordID=1349&UserID=230 (Registration No. CRD42011001349)

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INTRODUCTION

Recent epidemiological studies estimate a prevalence of 1:100 for autism spectrum disorder (ASD) [1], ~~which is a surprising~~an increase over reported rates ~~reported~~ in the past [2]. There has been increasing interest in developing effective interventions for young children with ASD, since the evidence suggests that early intervention programmes are indeed beneficial for children with ASD, often improving developmental functioning and decreasing maladaptive behaviours and symptom severity [3], and also can improve outcomes in later years for many ~~most~~ individuals [4].

An increasing volume of published trials of psychosocial intervention programmes for preschool children with ASD have been seen in recent years. These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA) (e.g. [5]); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism (e.g. [6]); iii) multimodal interventions targeted across areas of autistic children's development (e.g. [7]). In addition, an increasing number of these studies have followed CONSORT guidelines [8], and some meta-analyses and systematic reviews about intervention programmes for preschool children with ASD have been published; e.g. [9-11]. These meta-analyses and systematic reviews focused exclusively on one or the others of these groups of intervention styles; there has been no systematic review or meta-analysis of studies comparing results from different types of intervention approach from the viewpoint of the three models. For clinicians and commissioners this poses a difficulty in making general choices in a field containing often strong and partisan claims of effect from different traditions of intervention. Related to this, there has been great variation in endpoint measures used in these reported studies, making ~~the~~ comparisons of ~~the~~ effects between studies difficult. Specifically, there has been variation in whether endpoints have been framed in terms of specific autism symptom outcomes, non autism-specific

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outcomes that are not specific to autism (such as for instance IQ), or 'intermediate' ~~developmental~~ endpoints relating to aspects of development that may have some relationship to later autism symptoms – examples would be changes in joint attention or parent-child interaction. These ~~; and these~~ latter two kinds of outcome are ~~have~~ often ~~been~~ reported, without necessarily strong justification, as if they were the equivalent of change in autism symptoms (~~ie~~i.e. as 'surrogate' endpoints); and this can cause real confusion~~. for autism specific symptoms or disorder.~~ We think that these considerations indicate the need for a more comprehensive review of intervention studies for preschool children with ASD, covering studies of adequate quality across different intervention types and measurement methods, with a view to identifying the best current evidence for preschool interventions in the disorder. In this study, we will investigate it by comparing three major types of interventions with various outcomes.

We will undertake a systematic review and a meta-analysis of RCTs for preschool children with ASD. Recently, many RCTs for children with ASD have ~~been~~ emerged ~~as~~ sufficient enough ~~as~~ to perform meta-analyses. RCT methodology has been identified as the gold standard in efficacy research [12]. In addition, meta-analyses of RCTs is at the top ~~hierarchy~~ of the evidence based medicine hierarchy [13]. Thus, the findings of this study will ~~be very~~ provide strong evidence about interventions for children with ASD. Howlin et al. are asserting that there are three main strands of early interventions for children with ASD): programmes with a particular emphasis on the use of behavioural principle to improve learning and behaviour; those that have a specific focus on communication; and those in which developmental/educational strategies have been employed [14]. In this study, we named those strands as behavioural, communication-focused, and multimodal developmental interventions, respectively. ~~We classify the interventions for preschool children with ASD under the three models; i.e. behaviour model, developmental model, and communication focused model.~~ Understanding the mechanisms that underlie this

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attenuation of treatment effects and how these can be overcome is one current challenge [15]. This study may reveal each type of the intervention's strong and weak points~~This study will reveal which type of interventions is the most effective~~ to various kinds of treatment factors respectively. Its findings will guide us to develop new types of interventions to overcome the attenuation of treatment effects in the core symptoms of autism. It will contribute to the appropriate choices of the interventions for children with ASD for their families, clinicians, and the policymakers.

The objective of our study is to: i) conduct a systematic review of all the preschool intervention literature in ASD, including the type of intervention that is being tested and classification of outcome measures used; ii) to undertake a meta-analysis of methodologically adequate studies using the Cochrane tool, which will allow for the first time comparison of different approaches to intervention on comparative outcome measures.

METHODS

Types of studies

We will include ~~randomized~~ randomised controlled trials and subject these to a rating on the Cochrane Collaboration tool for assessing risk of bias~~quality criteria~~.

Types of participants

Participants comprise preschool children aged 0 to 6 with a diagnosis of ASD as below.

Diagnostic and statistical Manual of Mental Disorders-Ⅳ-Text Revision (DSM-Ⅳ-TR) [16]

- Autistic disorder
- Asperger disorder

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- Pervasive developmental disorder not otherwise specified (PDD-NOS)

International Classification of Diseases-10 (ICD-10) [17]

- Childhood autism
- Asperger syndrome, atypical autism
- Other pervasive developmental disorders
- Pervasive developmental disorders, unspecified.

~~Participants comprise preschool children with a diagnosis of autism spectrum disorder (ASD) aged 0 to 6.~~

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Types of interventions

We classify interventions for preschool children with ASD in three groups; i) behavioural interventions – based essentially on learning theory and on applied behaviour analysis; ii) communication-focused interventions, targeting social communication impairment, as the core symptom of autism; iii) multimodal developmental interventions targeting a range of aspects of children's development.

Types of outcome measures

A feature of this review is that we will systematically classify the various outcome measures used within recent intervention trials into the following categories:

Primary outcomes

Autism behavioural symptoms: qualitative impairment in social interaction; qualitative impairment in communication; restricted repetitive and stereotyped patterns of behaviour, interests, and activities. These are the triad of diagnostic criteria for autism in DSM-Ⅳ-TR and the definitional symptoms of the disorder and key indicators of

psychopathology (e.g. the autism Diagnostic Observation Schedule-Generic [18] will be used for these outcomes.).

Secondary outcomes

Non-specific developmental outcomes. These are not directly related by definition to autism diagnosis but are used in some studies as substitute outcomes – examples are adaptive behaviour (e.g. the Vineland Adaptive Behaviour Scale [19] will be used for this outcome), and IQ and cognitive development (e.g. the Wechsler Preschool and Primary Scale of Intelligence third edition [20] will be used for these outcomes.).

Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples (along with appropriate measures) are: measures of joint attention (the Early Social Communication Scales [21]), imitation ability (the Imitation Battery [22]), symbolic play (the Communication and Symbolic Behaviour Scales Developmental Profile [23]), parent-child interaction (the Dyadic Communication Measure for Autism [24]), receptive language (the MacArthur-Bates Communicative Development Inventory (MCDI [25])), expressive language (MCDI [25]).

~~Intermediate outcomes relevant to the known development of autism – which might be candidates for surrogate endpoints. These outcomes are often defined as the proximal targets of intervention approaches from a developmental perspective. Examples are: measures of joint attention, parent child interaction, imitation ability, symbolic play, social communication in an interactive setting, receptive language, expressive language.~~

Electronic searches

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We will do a systematic review of the published work according to the PRISMA statement [26]. Relevant studies will be identified by searching the following data sources: PsycINFO (from 1956 to January, 2011), Medline via Ovid (from 1950 to January, 2011), ERIC (from 1950 to January, 2011) and the Cochrane database.

We will use the following search terms to search all trials registers and databases: "autism" , "autism spectrum disorder", "ASD", "high function autism", "high function ASD", "Asperger syndrome", "pervasive developmental disorder", "PDDNOS", "intervention", "treatment", "therapy", "communication", "interpersonal", "speech", "interaction", "synchrony", "relationship", "language", "social", ~~and~~ "development", "behavior ~~therapy~~", "intensive behavioral intervention", "trial", and "outcome". Their search will be limited by age group from 0 to 6 years old and "randomized controlled trial." This search strategy has been peer-reviewed by a librarian of University of Manchester.

Validity assessment

Two of the authors, Y.T., Y.H. ~~independently~~ will independently review the abstracts of the potentially ~~the~~ relevant studies. This will be followed by a consensus discussion with J.G. The quality of the RCTs will be coded independently by Y.T. and Y.H. and disagreements will be resolved by consensus discussions.

Searching other resources

Reference lists from identified trials and review articles will be manually scanned to identify any other relevant studies. The clinicalTials.gov and the Cochrane Library website will be also searched for ~~randomized~~ randomised trials that were registered as completed but not yet published.

Data collection and analysis

Selection of studies

Inclusion:

1. Participants comprise preschool children with a diagnosis of ASD or pervasive developmental disorder (PDD).

2. ~~Randomized~~ Randomised controlled trials

3. Interventions delivered to the parents/guardians and/or directly to the child, by special educators, teachers, speech pathologists, psychologists, or other allied health professional students will be included.

4. Studies carried out while the children were at a preschool age between 0 and 6 years.

~~5. The control group will be those who did not received early intervention for autism.~~

~~6. Studies judged to be in low risk of bias according to the Cochrane Collaboration tool for assessing risk of bias~~

Exclusion:

1. The study was not primary research on preschool children with ASD~~autism~~.

2. The study did not assess a cognitive/behavioural intervention for preschool children with ASD~~autism~~.

~~3. The study did not report adequately on any measurable data for health related outcomes relevant to the review.~~

3~~4~~. The study design was not a randomis~~zed~~ed controlled trial.

4~~5~~. ~~The intervention used alternative medicine.~~ Alternative or complementary medicine was used as the main intervention of the study.

5~~6~~. The intervention was a pharmacological one.

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67. The intervention was not classified into behavioural, multimodal developmental or communication-focused model.

78. The control group received ~~–~~a specific early intervention programme for children with autism which was not a usual treatment provided by their local services.~~some early intervention for children with autism.~~

89. ~~Studies~~ The study was judged to be in high risk of bias by ~~according to~~ the Cochrane Collaboration tool for assessing risk of bias.

All citations sourced from the search strategy will be transferred to EndNote, a reference management database software. Initial screening of titles and abstracts by an experienced research fellow (YT) will eliminate all those citations obviously irrelevant to the topic, for example, prevalence studies, studies not relating to autism spectrum disorders, single case studies. Thereafter, two review authors (YT and YH) will assess and select studies for inclusion from the group of superficially relevant studies. In the event of a disagreement, resolution will be reached in discussion with the third author (JG), if necessary following inspection of the full paper.

Data extraction and management

YT and YH will independently extract data from selected trials using a specially designed data extraction form. Extracted data will consist of methods (dose and frequency of intervention); diagnostic description of participants, and type of intervention, including target, intensity, duration and method of application (parent-mediated, therapist, school-based etc.). Data will be extracted independently by two review authors (YT and YH) and disagreements will be resolved by negotiation with a third author (JG).

Assessment of risk of bias in the studies

Risk of bias will be assessed by two independent review authors (YT and YH) and disagreements will be resolved by negotiation with a third review author (JG). We will use the Cochrane Collaboration tool for assessing risk of bias in these areas [27]. The assessed risk of bias in studies will include in the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other sources of bias. The process will involve recording the appropriate information for each study (for example describing the method used to conceal allocation in detail) and evaluating whether there is risk of bias in that area (for example, was allocation adequately concealed). We will allocate studies to the three categories according to our judgment of each area or potential risk of bias: A. Low risk of bias; B. Moderate (or unclear) risk of bias; C. High risk of bias. Whether the studies should be included for the analyses or not will be judged individually based on the results of the risk of bias assessments.

Measures of treatment effect

Continuous data

Continuous data will be analysed on the basis that the means and standard deviations are available and that there is no clear evidence of skew in the distribution.

~~**Measures of treatment effect**~~

~~The categories of outcome measure differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims for the first time to make comparison across these different types of intervention study, thus we will standardize and synthesize the various categories of outcome measure using an inverse variance method. The measures used~~

~~for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses, comparing type of intervention model effectiveness for each outcome using a standardized mean difference. This is a novel approach for this field.~~

Dealing with missing data

Missing data will be assessed for each individual study. Where a loss of significant quantities of participant data is reported such that the review authors agree that the conclusions of the study are compromised, trial authors will be contacted. If no reply is forthcoming or full data are not made available, these studies will not be included in the final analysis. For included studies reporting drop-out, we will report the number of participants included in the final analysis as a proportion of those participants who began the intervention. Reasons for missing data will be reported. The extent to which the results of the review could be altered by the missing data will be assessed and discussed. If summary data are missing, trial authors will be contacted. If no reply is forthcoming or the required summaries are not made available, the authors will include the study in the review and assess and discuss the extent to which its absence from meta-analysis affects the review results.

Assessment of heterogeneity

Consistency of results will be assessed visually and by chi-square tests [28]. In addition, since chi-square can have low power when only few studies or studies of a small sample size are available [29], we will use the I^2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis [30].

~~Consistency of results will be assessed visually and by a Chi2 test. If the meta-analysis includes only a small number of studies, or where studies have small sample sizes, a P value of 0.10 will be applied for statistical significance. In addition, since Chi2 can have low power when only few studies or studies of a small sample size are available, we will use the I2 statistic to calculate the degree to which heterogeneity is having an impact on the analysis (Higgins 2008).~~

Assessment of reporting biases

If sufficient studies are found, funnel plots will be drawn to investigate any relationship between effect size and sample size. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. If a relationship is identified, clinical diversity of the studies will be further examined as a possible explanation. Every attempt will be made to obtain unpublished data and data from conference proceedings.

Data synthesis

Data synthesis will be performed using Review Manager version 5.1 (Cochrane Collaboration software). We will assess continuous and binary data. Assuming that two or more studies that are suitable for inclusion are found, and that the studies are considered to be homogenous, a meta-analysis will be performed on the results. The categories of outcome measure mentioned above differ conceptually in important ways, and have been used in a systematic different way across trials of the different intervention types identified above. Our review aims to make comparison across these different types of intervention study, thus we will standardis~~z~~e and ~~synthesize~~ synthesise the various categories of outcome measure using an inverse variance method in a

random effect model[30]. ~~The measures used for outcome are varied between studies and the standardized data will be heterogeneous. We will use a random effects model for the analyses~~ [30]~~, since we do not assume that each study is estimating exactly the same quantity.~~ We will compare the types of intervention model effectiveness for each outcome using a ~~standardized~~ standardised mean difference.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses and meta-regression ~~and where no significant heterogeneity of effect sizes is found.~~ T~~t~~hese will be pooled to calculate a final effect size. While these analyses may enable us to ~~hypothesize~~ hypothesise as to possible causes of differences between studies' findings, some heterogeneity is likely to remain, and any statistical analysis will be accompanied by a narrative synthesis.

Subgroup analysis will be undertaken if clinically different interventions are identified, or there are clinically relevant differences between participant groups. Anticipated clinically relevant differences are:

1. intervention delivery type (e.g. therapist, parent-mediated, school-based) and length
2. intervention target skill (e.g. Theory of Mind as a whole, joint attention, emotion recognition, false belief understanding)
3. participant age (e.g. preschool, young children~~, adolescents, adults~~), IQ (low versus normal or high), specific diagnosis and verbal ability.

Relevant subgroup analyses will also include:

·Severity of autism at baseline~~. This is a crucial element in evaluating autism studies.~~

·Social economic status ~~SES~~ and other demographic variables~~.~~

~~Sampling bias and external validity of studies is an important consideration.~~

·Age of child

·Type of intervention (our 3 groups as above)

·Parent-mediated (directing parents to train their children, not training the children directly) vs. child-mediated (training the children directly) intervention delivery

~~. A key distinguishing point between different studies in the area.~~

·Cognitive ability at baseline

Sensitivity analysis

Sensitivity analysis will be conducted to assess the impact of study quality on the results of the meta-analyses. For example, we will test to see if studies with high rates of loss to follow up or inadequate blinding are more likely to show positive outcomes and also to assess the impact of imputing missing data.

DISCUSSION

~~This study will provide the most reliable basis for decisions on early intervention for preschool children with ASD.~~We believe that the findings of this systematic review and meta-analysis will have important implications for both clinical practice and research. Meta-analysis of ~~randomized controlled trial~~RCTs across types of intervention ~~of the interventions~~ for preschool children with ASD is an important step in providing a ~~will can provide a more the most~~ reliable basis for ~~the~~ implementation decisions ~~of early interventions for them~~. Since previous analyses have been essentially restricted to specific intervention types, and often with different outcome criteria, a study ~~Analyses as to~~ across ~~the~~ three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD. This study will provide information about which kind of intervention has ~~strength~~ strong points and weak points, and what are those ~~strength~~

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strong points and weak points are. This study may also suggest what kinds of elements future intervention programmes for children with ASD should have. ~~This study may also reveal what points are lacking among the current intervention programmes for children with ASD.~~ We strongly believe those findings will be able to translated into the clinical practices and patients and their family benefits. Anticipated challenges in synthesise the literature exist. The measures used for outcome are varied between studies and the standardised data will be heterogeneous. We do not assume that each study is estimating exactly the same quantity. Thus, we will use random effect models for the analyses[30]. In addition, the durations of the interventions will be different among the studies included in this study. We will synthesise the data regardless of the durations of the interventions, and will discuss the diversity of the durations in our paper.

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Authors' contribution YT and JG contributed to draft the protocol and develop a search strategy. YT also drafted this manuscript. RE contributed to provide statistical advice for the design and the analysis. All authors read and approved the final manuscript.

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Competing interests None.

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