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TABLE OF CONTENTS

[Intervention Protocol]

Family therapy for autism spectrum disorders

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the clinical effectiveness and acceptability of family therapy as a treatment to enhance communication or coping for individuals with ASD and their family members. If possible, we will also seek to establish the economic costs associated with family therapy for this clinical population.

BACKGROUND

Description of the condition

Autism spectrum disorders (ASD) are a cluster of childhood onset neurodevelopmental conditions characterised by qualitative impairments in communication, reciprocal social interaction, and restricted and repetitive interests and behaviours (WHO 1992). There is substantial heterogeneity in the ASD symptom profile and clinical presentation; hence, diagnosis is often not made until late adolescence or adulthood (NICE 2012). Once thought to be fairly rare, current prevalence estimates indicate that ASD is relatively common, affecting at least 1% of the population (Brugha 2011).

The degree of impairment resulting from core ASD characteristics varies widely. Educational attainments are often poorer for younger people with ASD in comparison to typically developing peers (Levy 2011). Similarly, the adult ASD population experiences significant difficulty with gaining and sustaining meaningful employment (Howlin 2013; Mavranezouli 2014). A lack of peer and intimate relationships are frequently the norm (White 2009a), leading to diminished social opportunities beyond those that stem from the family network, social isolation, and loneliness. Daily living and self sufficiency skills can also be impeded, and individuals with ASD often depend on ongoing support from family members well into adulthood (Gray 2014; Magiati 2014). ASD are commonly associated with learning disability and high rates of psychiatric comorbidity (Hofvander 2009; Joshi 2013;

Simonoff 2008), including anxiety disorders (Van Steensel 2011; White 2009b), depression (Ghaziuddin 2002), attention deficit hyperactivity disorder traits (Taylor 2013), and more general "emotional and behavioural problems" (Maskey 2013). Comorbidities further compound difficulties across multiple domains of functioning and exacerbate reliance on family members as well as carer stress and burden (Cadman 2012).

The experiences and needs of family members of individuals with ASD have garnered increasing attention in recent years. Findings from epidemiological and genetic studies indicate that ASD is a highly heritable condition (Hallmayer 2011; Lichtenstein 2010; Lundström 2010). Also, studies have found that parents of people with ASD can present with higher levels of stress, distress, fatigue, anxiety, and depression symptoms than those reported for parents of typically developing or other clinical populations (Cadman 2012; Firth 2013; Giallo 2013; Hoefman 2014). Additionally, research findings suggest that carers can experience concerns about their parental efficacy and coping (Karst 2012). There has been some, albeit limited, research about siblings of individuals with ASD. Tentative study findings suggest that some siblings may experience slightly elevated levels of "behavioural problems" compared to non-clinical populations (Hastings 2014), or features of anxiety (Shivers 2013). Sibling adjustment and relationships may be affected by the severity of ASD and associated symptoms (Petalas 2012). Siblings may also be expected to take on more household duties (for example, chores), or more responsibility (for example, informal caregiving) compared to the individual with ASD, although this is not a consistent finding across studies (Meirsschaut 2011).

Description of the intervention

Family therapy can be defined as a formal psychotherapeutic intervention that seeks to understand and enhance relationships, communication, and functioning between members of a family (Dallos 2010). While there are several types of family therapy, they are predominantly underpinned by systemic theories and share central tenets (Hayes 1991). First, it is proposed that various problems, such as mental health functioning or the development and maintenance of interpersonal relationships, are contextually bound (that is they are likely to be predisposed and perpetuated by the context and system(s) within which they occur, rather than solely being attributed to the individual themselves) (Dallos 2010). Second, it is suggested that societal and cultural norms, values, and expectations influence and shape familial beliefs and behaviours both collectively (that is the intergenerational family unit) and individually, and that problems are best understood and addressed in terms of these influences. Third, it is hypothesised that the family unit and the relationships between family members are dynamic (that is that the reactions and responses of one person affect those of others in the system, in a bi-directional fashion, linearly and longitudinally). Fourth, families are said to develop ways of coping with periods of change and transition (for example, births, marriages, and bereavements), and illness or adversity, in order to maintain stability as a unit (Goldenberg 2012). Oftentimes these patterns of coping are adaptive and shared between all family members, yet on occasion, individuals (within the family) may adopt distinct coping styles leading to communication and relationship difficulties. Finally, it is considered that there are commonalities in the ways that family members use language and narratives to converse and make sense of their own and others' experiences, but also subtle differences, which in turn may lead to or exacerbate ambiguity, misinterpretation, or disagreements.

Family therapists use a range of interventions (Dallos 2010), including psychoeducation; development of genograms to map out cultural, resilience, or other familial patterns (Butler 2008); narrative techniques (for example, to explore language, meanings, and attributions) (Carr 1998); and the use of particular questioning styles (for example, circular and reflexive questions to enhance the breadth and depth of discussion) (Hayes 1991). In clinical practice, individuals presenting for family therapy may be part of the same family or part of the wider friendship group. Individuals are encouraged to decide for themselves who can and will engage in treatment, and the configuration of those attending may vary from session to session. The duration of therapy can be several weeks to several months. Choices about the number of sessions to offer are largely dependent on the service model and constraints, familial presenting needs, and the therapist's theoretical stance.

How the intervention might work

Family therapy for ASD can be hypothesised to work in several ways (Solomon 2012). Individuals with ASD and family members can be supported to understand and make sense of the diagnosis (for example, through the use of psychoeducation). Discussion can be facilitated about preferences for using different terminology to describe the core symptoms (for example, autism spectrum 'disorder' or autism spectrum 'condition') and the narratives and meanings that arise from this for individuals and the family unit collectively. The impact of core characteristics (for example, engagement in routines or impairments in socioemotional reciprocity such as a lack of empathy) can be explored with a view to reducing feelings of frustration or annoyance. Interventions can encourage discussion about broad factors and familial patterns or responses that may contribute to difficulties with communication and relationships or challenging behaviour, and support the identification of strategies to promote cohesion within the system. Family therapy can also encourage open dialogue between carers (for example, about potential guilt or feelings of stress or worry), and in turn, strategies can be developed to enhance marital relationships, resilience and coping, and positive parental mental health. Family therapy also provides a supportive therapeutic space for siblings to explore their concerns or unanswered questions (for example,

about heredity factors or their current and potential prospective role as a carer).

Why it is important to do this review

ASD are common, lifelong disorders characterised by overt and subtle qualitative impairments in communication, social interaction and relatedness, and preferences for engaging in restricted interests and repetitive behaviours (WHO 1992). Difficulties with tolerating uncertainty, ambiguity, and change within and beyond the immediate environment are additional hallmark characteristics (APA 2013). Core ASD symptoms can impact significantly on daily social and occupational functioning during childhood and adulthood. Individuals with ASD may find it difficult to initiate and sustain interactions with others despite the desire for relationships (and increased social opportunities). Also, symptoms of ASD typically impact others in the family (Hoefman 2014). Parents (carers) and siblings often must accommodate restricted interests and adherence to seemingly non-functional routines. Inherent difficulties with communication and interaction can adversely affect relationships with, and between, family members. The need to provide intensive and ongoing support to individuals with ASD can incur stress, anxiety, and depression in carers, as well as poor perceived parental efficacy and coping (Karst 2012).

There is no cure for ASD per se, and the heterogeneity of the disorder negates the use of monotherapy. Instead, the more parsimonious approach is to develop combinations of interventions that 1) reduce or ameliorate the effect and impact of core ASD symptoms, and 2) support individuals and others around them to enhance their repertoire of skills (Smith 2014; Woodman 2015). Further, interventions are needed across the lifespan to address the needs of children as well as adults with ASD. There is promising evidence for the use of psychological interventions for individuals with ASD, such as behavioural and cognitive-behavioural (Lang 2010; Spain 2015a; Sukhodolsky 2013), social cognition (Fletcher-Watson 2014), and skills-based interventions (Reichow 2013; Spain 2015b), but a limitation to these approaches is that they do not explicitly address relationship and communication issues between family members, nor do they seek to enhance familial coping strategies or resilience factors. Similarly, a recent review has highlighted the potential effectiveness of parent training for ASD (Oono 2013), but this approach encourages parents to take on a more facilitative role, rather than specifically targeting their (potential) concurrent needs and the bi-directional relationship between individuals. Conversely, family therapy is a more inclusive intervention and has been found to be effective for different clinical populations (Carr 2009). Whether the structure or content of family therapy for individuals with ASD requires adaptation (as is the case for other psychological therapies), for example to accommodate the impact of inherent impairments, is not wholly clear. Undertaking a systematic review of the empirical data is important in order to:

1. ascertain the potential effectiveness and acceptability of formal family therapy work for individuals with ASD;
2. establish whether there are integral features of these approaches that are associated with improved outcomes; and
3. consider how best interventions can be tailored to the specific lifelong needs of this clinical population and their family members.

OBJECTIVES

To evaluate the clinical effectiveness and acceptability of family therapy as a treatment to enhance communication or coping for individuals with ASD and their family members. If possible, we will also seek to establish the economic costs associated with family therapy for this clinical population.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised controlled trials (q-RCT) (in which participants are allocated by alternate allocation, for example, according to days of the week). We will exclude cross-over trials due to the issue of carry-over.

Types of participants

Families which have at least one person -- child or adolescent (aged 17 years and under) or adult (aged 18 years and over) -- diagnosed with an ASD.

We will define autistic spectrum disorder according to clinical criteria of either the International Classification of Diseases, WHO 1992, or the Diagnostic and Statistical Manual for Mental Disorders, APA 2013, and ideally (but not necessarily) diagnosed using standardised methods of assessment (for example, the Autism Diagnostic Interview-Revised, Lord 1994, or the Autism Diagnostic Observation Schedule, Lord 2000).

We will define family members as individuals from multigenerations (parents, grandparents, siblings, children, or spouses), who are either biologically related to the individual with ASD, or related through marriage or cohabitation. We will also include non-professional carers (for example, individuals who provide foster or respite care) and significant others, such as friends.

We will include studies that describe interventions delivered to participants residing in the same dwelling, or interventions that are offered to family members who live separately.

We will not exclude studies where participants have a comorbidity or are receiving other treatments concurrently to the family therapy, although we will endeavour to clarify this level of detail from reports or by contacting trial authors.

Types of interventions

Family therapy

We will include family therapy interventions delivered by at least one suitably qualified clinician, which are derived from systemic theories, and specifically focus on understanding, enhancing, and improving aspects of relationships between individuals with ASD and at least one family member; or between two or more members of the family of an individual with ASD (for example, parents, or parents and siblings). We will include the following modalities of family therapy: systemic therapy; structural family therapy; strategic family therapy; Milan approaches; solution-focused therapy; narrative therapy; and behavioural family therapy. The intervention can be offered either face-to-face or via web-based real-time sessions. We will exclude studies that describe pure bibliotherapy, psychoeducation, or parent training techniques. There is no stipulation regarding the number or duration of sessions delivered.

Control condition

We will include four main types of comparator interventions:

1. no treatment;
2. provision of standard clinical care (i.e. treatment as usual);
3. a wait-list control (e.g. a delayed-start intervention); and
4. an active comparator (e.g. an alternative psychological intervention such as applied behavioural analysis or cognitive behavioural therapy).

Types of outcome measures

We have identified primary and secondary outcomes for individuals with ASD and family members. We will include outcome measures that generate either dichotomous or continuous data. To be eligible for inclusion, outcome measures will need to be standardised and validated. While measures may not necessarily have been specifically validated for use with the ASD population, many intervention studies that include participants with ASD utilise measures (for example, self report questionnaires) that have been validated in non-ASD samples (Lang 2010; Reichow 2013; Spain 2015a; Spain 2015b). We will describe the psychometric properties of outcome measures where possible, and highlight whether there are indicative normative thresholds (that is cut-off scores) for ASD samples.

Outcome measures can be completed by individuals with ASD, family members, or via objective (clinician-administered) instruments. We will include outcome measures that have been completed at different time points, including postintervention or at follow-up; and those outcomes that relate to short-term changes (such as attributions about coping or satisfaction with the intervention), and longer-term outcomes (such as direct and indirect costs).

Primary outcomes

1. Quality or quantity of social interaction and communication (e.g. Social Responsiveness Scale by Constantino 2003; Autism Diagnostic Observation Schedule by Lord 2000).
2. Mental health morbidity, including stress, anxiety or depression (e.g. Hospital Anxiety and Depression Scale by Zigmond 1983).
3. Quality of life (e.g. EQ-5D by Szenda 2007), including quality of relationships with family members (e.g. Family Questionnaire by Wiedemann 2002).
4. Adverse effects or events (e.g. increased mental health morbidities, as measured by the Hospital Anxiety and Depression Scale; or an increase in challenging behaviour).

Secondary outcomes

1. Confidence in or attributions about coping (e.g. Attributional Style Questionnaire by Seligman 1984).
2. Satisfaction with treatment (e.g. Client Satisfaction Questionnaire by Attkisson 1982).
3. Drop out from treatment.
4. Health economic outcomes, including direct costs (e.g. treatment costs) and indirect costs (e.g. use of clinical services or work absence due to stress).

Search methods for identification of studies

We will use a search strategy that combines two concepts: the condition (ASD) AND intervention (family therapy). We will not limit the search by language, date, or publication status, and we will seek translation of documents where necessary.

Electronic searches

We will search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL), part of the *Cochrane Library*, current issue (and which includes the specialised register of the Cochrane Developmental, Psychosocial and Learning Problems Group).
2. Cochrane Database of Systematic Reviews, part of the *Cochrane Library*, current issue.
3. Ovid MEDLINE, 1946 to current.
4. Embase (Ovid), 1980 to current.
5. CINAHLPlus (EBSCOhost), 1937 to current.
6. PsycINFO (Ovid), 1806 to current.

7. Education Resource Information Center (ERIC) (EBSCOhost), 1966 to current.
8. Sociological Abstracts (ProQuest), 1952 to current.
9. Dissertation Abstracts International (ProQuest).
10. UK Clinical Research Network Study Portfolio (UKCRN) (public.ukcrn.org.uk/).
11. ClinicalTrials.gov (clinicaltrials.gov).
12. World Health Organisation (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/default.asp).
13. AutismData (autism.org.uk/autismdata).

We will use the strategy for Ovid MEDLINE, shown in Appendix 1, and modify it as appropriate for other databases.

Searching other resources

We will undertake additional searches as follows: 1) we will hand-search the reference lists of included studies and seminal texts cited in the protocol; and 2) we will contact experts, including researchers who have undertaken studies in the field, to ask if they know of any studies not already identified by the searches.

Data collection and analysis

Selection of studies

Selection of studies will involve several steps. We will initially import all citations retrieved from the searches into EndNote (an electronic programme used to manage references, EndNote X7). After removing duplicates, DS and JS will independently screen the list of titles and abstracts for relevance. DS and JS will obtain and inspect full reports of any studies that appear relevant, or for which more information is needed, and then independently assess each text for eligibility based on the above inclusion criteria. To enhance reliability, EP will independently review a random 25% of the total sample of all abstracts obtained, and a random 25% of all full-text reports retrieved. If disputes arise, such as regarding the relevance of titles, abstracts, or full reports, we will contact report authors to provide clarification, or FH will provide further consultation, or both. With as much as possible information obtained from the aforementioned sources, any disputes will be resolved through discussion by the review authors, until consensus is reached.

Data extraction and management

DS and JS will independently extract data. To enhance rigour, EP will also independently extract data for a random 25% of studies. We will extract data onto standardised forms using Microsoft Excel before entering the relevant data into Review Manager software (RevMan 2014).

The data extraction form will include subheadings relating to the following areas.

1. Study methods (including methods of randomisation, allocation concealment, and blinding of research personnel or participants).
2. Ethical approval (provision of informed consent or assent).
3. Referral route (method through which individuals are referred/present for family therapy).
4. Participant demographics and clinical diagnoses (including ASD and comorbid diagnoses).
5. Instruments used to diagnose ASD (including clinician-administered assessments with either participants or informants).
6. Active and comparator interventions (modality, content, and duration of the active and comparator interventions).
7. Outcome measurements (for individuals with ASD and their family members; and health outcome data if cited).
8. Results (including descriptive and inferential statistical data, as well as study results).
9. Adverse events (e.g. whether there has been an increase in mental health morbidities).
10. Treatment fidelity (e.g. whether a manualised treatment approach was used, if treatment sessions were independently reviewed for adherence to the theoretical model, and the frequency and nature of clinical supervision for trial therapists).

We will attempt to separate the outcomes and results between sites for any multicentre studies. In the event that data described appear ambiguous for any of the reports, we will contact the authors for clarification. If we are unable to liaise with report authors, we will document this within the review, and the review team will discuss the discrepancies.

For any non-English language studies, we will endeavour to arrange for report translation.

Assessment of risk of bias in included studies

DS and JS will independently assess the risk of bias of all included studies across six domains: random sequence generation; allocation concealment; blinding (of participants, trial staff, and completion of outcome assessments); incomplete outcome data; selective outcome reporting; and any other potential sources of bias. For each included study, we will assign each of these domains one of three ratings: high risk of bias; low risk of bias; or unclear risk of bias. We have detailed criteria for rating various domains of bias below, with examples drawn from Chapter 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Random sequence generation

1. High risk of bias: a non-random method is used to generate the sequence, such as allocation by alternate days or geographical location of entry to the trial.

2. Low risk of bias: random methods (e.g. random number table or computer random number generator) are used to generate the sequence to produce comparable groups.

3. Unclear risk of bias: no or insufficient information is provided on the methods used to generate the sequence to permit a judgement of high or low risk of bias.

Allocation concealment

1. High risk of bias: participants and researchers may have been able to foresee assignment to intervention groups due to insufficient measures used to conceal allocation (such as open random allocation schedule, unsealed or non-opaque envelopes).

2. Low risk of bias: adequate methods are used to conceal the allocation (e.g. opaque envelope procedure, central allocation or by independent personnel outside of the research team) so that participants and researchers are unable to foresee or influence the assignment of intervention groups.

3. Unclear risk of bias: no or insufficient detail is provided on methods used to conceal the allocation sequence to permit a judgement of high or low risk of bias.

Blinding of participants and research personnel

1. High risk of bias: neither participants nor research personnel are blinded to the treatment group allocation or study hypotheses, and outcomes are likely to be influenced by such lack of blinding; or blinding is attempted and subsequently broken; or some participants and personnel are blinded while others are not blinded, which may introduce bias.

2. Low risk of bias: effective measures (e.g. placebo or sham therapy sessions) are used to blind study participants and research personnel from knowing intervention group allocation and study hypotheses; or when blinding is not possible, study authors are able to justify that the outcome is unlikely to be influenced by the lack of blinding.

3. Unclear risk of bias: either the study did not address this outcome or insufficient details are provided on methods of blinding to permit a judgement of low or high risk of bias.

Blinding of outcome assessment

1. High risk of bias: outcome assessors are not blinded to treatment allocation of the study participants and the study hypothesis, and the outcomes are likely to be influenced by lack of blinding.

2. Low risk of bias: objective measures (such as biomedical measures of cortisol levels) that are unlikely to be influenced by the lack of blinding outcome assessors are used; participants are unaware of which intervention they have been allocated to; or participants' knowledge of which intervention they are receiving does not mediate their response to subjective outcome measures.

3. Unclear risk of bias: there is a lack of detail on methods of blinding to permit a judgement of high or low risk of bias.

Incomplete outcome data

1. High risk of bias: reasons for missing data are likely to be related to the true outcome; missing data are not balanced across groups; or inappropriate methods are used to impute missing data.

2. Low risk of bias: no incomplete outcome data for each main outcome; reasons for missing data are unlikely to be related to true outcome; missing data are balanced across groups; or appropriate methods have been used to impute the data.

3. Unclear risk of bias: either the study did not address this outcome, or there is insufficient detail as regards to the amount, nature, and handling of incomplete outcome data to permit a judgement of low or high risk of bias.

Selective reporting

1. High risk of bias: not all prespecified outcomes are reported; or outcomes are reported using methods not prespecified and for only a subgroup of the sample; or outcomes are reported that were not prespecified; or outcomes are reported incompletely and cannot be included in a meta-analysis.

2. Low risk of bias: all outcomes are reported as prespecified in published protocol, or the protocol is not available, but there is convincing text that suggests that all prespecified outcomes have been reported.

3. Unclear risk of bias: there is insufficient information (e.g. no protocol available) to permit a judgement of high or low risk of bias.

Other sources of bias

1. High risk of bias: the study raises other important concerns, such as bias relating to the study design or claims of fraudulence, or other sources of bias that are not covered by the above domains.

2. Low risk of bias: there is no evidence to suggest there are any other important concerns about bias not addressed in the domains stated above.

3. Unclear risk of bias: there may be an additional risk of bias, but there is insufficient information to fully assess this risk, or it is unclear that the risk would introduce bias in the study results.

We will obtain a third opinion from EP, MF, or FH should there be disagreement about risk assessment or a lack of consensus about any of the individual domains per study or in terms of the overall appraisal of the trial. We will also attempt to contact report authors to provide clarification about aspects of the trial, as needed.

'Summary of findings' table

We will import data from Review Manager, RevMan 2014, into GRADEprofiler, GRADEpro GDT, and use this software to create 'Summary of findings' tables. These tables will provide outcome-specific information concerning the overall quality of the body of evidence from the studies included in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on outcomes rated as relevant to patient care and decision making.

We will employ the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence (Schünemann 2011), using the following ratings: high quality (RCTs or q-RCTs with a very low risk of bias), moderate quality (RCTs or q-RCTs with some evidence of risk of bias such as inadequate allocation concealment), low and very low quality (RCTs or q-RCTs that have significant threats to internal study validity such as failure to adequately randomise participants, lack of blinding of outcome assessors, or selective outcome reporting) (Higgins 2011, Table 12.2.a).

We will include the following outcomes in the 'Summary of findings' table.

1. Quality or quantity of social interaction or communication.
2. Mental health morbidity, including stress, anxiety, or depression.
3. Quality of life.
4. Confidence in or attributions about coping.
5. Adverse effects or events.

Measures of treatment effect

Dichotomous data

For dichotomous outcomes, such as the presence or absence of challenging behaviour(s), we will use the Mantel-Haenszel method for computing the pooled risk ratio (RR) (Mantel 1959). We will use the RR in meta-analyses, rather than the odds ratio (OR), because the OR can be susceptible to misinterpretation, which can lead to overestimation of the benefits and harms of the intervention (Higgins 2011, Section 9.4.4.4). We will report the RR with 95% confidence intervals (CIs).

Continuous data

Where different measures are used, we will calculate the standardised mean difference and 95% CI. We will calculate the mean difference and 95% CI where all outcomes are measured using the same scale in the same way.

Unit of analysis issues

Cluster trials

In cluster trials, the independence of individuals cannot be assumed (Higgins 2011). As we are examining the effectiveness of an intervention for both individuals and family members, we may identify cluster randomised trials.

If clustering has been incorporated into the analyses of primary studies, we plan to present these data as if from a non-cluster randomised study, but adjust for the clustering effect. We will contact study authors for more information if needed. If we identify cluster trials that have been analysed using incorrect statistical methods (that is not taking the clustering into account), we will contact study authors to request individual participant data so that we may calculate an estimate of the intracluster correlation coefficient (ICC). If we are unable to obtain this information, we will adjust sample sizes using an estimate of the ICC from the trial or from a trial of a similar population, with advice from a statistician, and use this to reanalyse the data. In the event that we are unable to adjust for incorrect statistical methods used by the cluster trials, and therefore cannot estimate the ICC with any a degree of confidence, we will exclude the trial (Higgins 2011).

We will investigate the robustness of our results by conducting sensitivity analyses, for example, to explore the impact of different types of cluster randomisation units (such as families, health practitioners) (Higgins 2011). We will also compare the results with and without cluster trials that have not been analysed correctly by the trialists (where the ICC is estimated from other trials for the adjustment of cluster effect) (see Sensitivity analysis).

Cross-over trials

Due to the issue of carry-over, that is whereby the effectiveness of a second intervention may be mediated by the first intervention, we will exclude cross-over trials.

Multiple comparisons

Where a trial involves more than two treatment (or comparator) arms, we will first assess which intervention (or comparator) groups are relevant to our review. We will use data from the arms of the trial that are relevant to the review objectives, but present all intervention groups in the 'Characteristics of included studies' tables, providing a detailed description of why we have selected particular groups and excluded others. In the event that studies have more than two intervention groups and a control group that are relevant to the review, we will split the control group data proportionately to the other two groups.

Repeated measures

Where a trial reports outcome data obtained at more than one time point, we will conduct analyses separately for each time point (for example, postintervention and at follow-up if follow-up is specified by the trialist).

Dealing with missing data

We will consider the possible impact of missing data on the results of the review.

Data may be missing either because (1) they have been insufficiently or inadequately reported, or (2) due to drop out/attrition. In the event of insufficient or inadequate reporting, we will first try to obtain any missing data from the trial authors, including unreported data (for example, group means and standard deviations (SDs)), details of dropouts, and interventions provided. We will describe the missing data in the 'Risk of bias' table.

In either case outlined above, and where we cannot obtain data, we will conduct analyses using intention-to-treat (ITT) principles. For dichotomous outcomes (those not deemed to be missing at random), we will impute the outcomes for the missing participants using both the most optimistic (that is assuming participants with missing data improve) and the most pessimistic (that is assuming participants with missing data deteriorate) scenarios.

Where data are missing for continuous outcomes (for example, data pertaining to means or SD), we will attempt to calculate them based on the standard errors, CIs, and t values, according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If this information is missing, and we are unable to obtain it from trial authors, we will report it as missing data in the review.

We will also conduct a sensitivity analysis to compare the results from the ITT analysis with the imputation and 'available case' analysis (see Sensitivity analysis). If these analyses yield similar results in terms of the effects of treatment, we will present the results of the available case analyses.

Assessment of heterogeneity

Within each comparison, we will first assess clinical heterogeneity (for example, variability in active and comparator interventions, participant characteristics, or outcome measures used) and methodological heterogeneity (for example, variability in study design, including differences in the nature of the randomisation unit and the size of cluster randomised; and risk of bias, which we will assess according to the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). If there is clinical or methodological heterogeneity, we will extract and document all of these characteristics onto the data extraction form and synthesise the results narratively. We will then assess statistical heterogeneity using the I^2 and Chi^2 statistics, and by visually inspecting the forest plots. If we identify a substantial level of heterogeneity in trials (for example, the I^2 is more than 30% to 60%, the P value is less than 0.10 in the Chi^2 test for heterogeneity, or there is a different direction of the effects), we will conduct prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We will assess reporting biases, including (multiple) publication, selective reporting, outcome, and language biases (Higgins 2011, Table 10.1.a). First, we will try to locate protocols of included trials. If the protocol is available, we will compare outcomes documented in the protocol and the published report. If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with the reported results. In addition, we will create funnel plots to investigate the possibility of publication bias and other small-study effects when there is a sufficient number of trials (10 or more). While funnel plots may be useful in investigating reporting biases, there is some concern that tests for funnel plot asymmetry have limited power to detect small-study effects, particularly when there are fewer than 10 studies, or where all studies are of similar sample size (Higgins 2011). In the event that funnel plots are possible, we will produce them and seek statistical advice in their interpretation.

Data synthesis

We will conduct random-effects meta-analyses to produce the average effect size of the intervention across trials. A random-effects model is considered more appropriate than a fixed-effect model because the population and setting of trials are likely to be different, and therefore the effects are also likely to be different (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

Depending on the sample size and heterogeneity of study populations, we propose to undertake subgroup analyses as follows:

1. Children and adolescents (aged 17 years and under) versus adults (aged 18 years and above) with ASD.
2. Individuals with ASD who have a concurrent learning disability (i.e. intelligence quotient (IQ) below 70) versus individuals with ASD and no learning disability.

To limit the risk of multiple comparisons, we will conduct subgroup analyses on primary outcomes only.

Sensitivity analysis

We will undertake sensitivity analyses to evaluate the impact of excluding trials (or trial data) that are judged to have a high risk of bias (for example, in terms of the domains of random sequence generation, allocation concealment, blinding, or outcome reporting). We will also undertake sensitivity analyses to assess the potential impact of missing outcome data.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

1. exp child development disorders, pervasive/
2. Developmental Disabilities/
3. pervasive development$ disorder$.tw.
4. (pervasive adj3 child$).tw.
5. (PDD or PDDs or PDD-NOS or ASD or ASDs).tw.
6. autis$.tw.
7. asperger$.tw.
8. kanner$.tw.
9. childhood schizophrenia.tw.
10. or/1-9
11. family therapy/
12. group therapy/
13. psychotherapy, group/
14. couples therapy/
15. marital therapy/
16. (systemic$ adj3 psychotherap$).tw.
17. (systemic$ adj3 psycho-therap$).tw.
18. (systemic$ adj3 famil$).tw.
19. (famil$ adj3 (intervention$ or therap$ or treat$ or program$)).tw.
20. (famil$ adj3 (psychotherap$ or psychoeducation$ or psycho-education$ or psycho-therap$)).tw.
21. ((marriage or marital or couple$) adj3 therap$).tw.
22. (famil$ adj1 (involv$ or integrat$ or participat$ or focus$)).tw.
23. (psychodynamic or psycho-dynamic).tw.
24. (group$ adj3 psychotherap$).tw.
25. (group$ adj3 psycho therap$).tw.
26. systemic therap$.tw.
27. solution focus$.tw.
28. (narrative adj1 therap$).tw

29. or/11-28
30. 10 and 29

CONTRIBUTIONS OF AUTHORS

DS: Review of proposal; design and preparation of the protocol. Will contribute to: screening of abstracts and studies; data extraction and quality appraisal of studies; initiating requests for further information from researchers who have undertaken potentially relevant studies; data analysis; and preparation of the review.

JS: Design and preparation of the protocol. Will contribute to: screening of abstracts and studies; data extraction and quality appraisal of studies; data analysis; and preparation of the review.

EP: Design and preparation of the protocol. Will contribute to: screening of abstracts and studies; data extraction and quality appraisal of studies; data analysis; and preparation of the review.

MF: Design and preparation of the protocol. Will contribute to: statistical advice and data analysis; and preparation of the review.

TC: Preparation of the protocol. Will contribute to: data analysis and preparation of the review.

DGM: Preparation of the protocol. Will contribute to: data analysis and preparation of the review.

FGH: Preparation of the protocol. Will contribute to: data extraction; statistical advice and data analysis; and preparation of the review.

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Eleni Paliokosta: None known.

Marie Furuta: None known.

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Declan G Murphy: None known.

Francesca G Happé holds positions related to her autism research for which she is not paid but which involve travel to meetings for which she is reimbursed. She also received royalties on books and chapters, and occasional honoraria for writing or presenting, but these support her autism research in general and do not conflict with or influence her impartial involvement in the current review. FGH supervises Debbie Spain's PhD, and her institution receives a grant from the NIHR to do so. FGH is the president and board member of the International Society for Autism Research and cofounder of the Forum for Neuroscience and Special Education. FGH's institution has received fees for her membership of the Methusalem grant review panel. Her institution has received grants from the UK Medical Research Council for a population-based twin study of autism spectrum disorders: genetic and environmental sources of cognitive and clinical heterogeneity; from the Baily Thomas Fund for work on the transition to young adulthood in autism spectrum disorder: mental health and well-being in a population-based sample of twins; the Wellcome Trust for work on glutamate and GABA in adults with autism: an in vivo study using magnetic resonance spectroscopy; and has grants pending from the Economic and Social Research Council for a topic not relevant to this review. FGH's institution has received honorarium from the British Academy for a lecture she carried out in 2014 and honorarium from the *Journal of Child Psychiatry and Psychology* for an invited annual review article. FGH receives royalties for the publications *Autism and Talent* and *Autism and Other Neurodevelopmental Disorders Affecting Cognition.* She has received travel/accommodation/meeting expenses from the British Psychological Society, Simons Foundation, and the University of Leuven.

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