Building capacity for rigorous controlled trials in autism: the importance of measuring treatment adherence

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Abstract

Research groups across Europe have been networking to share information and ideas about research on preschool children with autism. The paper describes preliminary work to develop capacity for future multi-site randomized controlled trials of early intervention, with a specific focus on the need to measure treatment adherence where parents deliver therapy. The paper includes a review of randomized and controlled studies of parent-mediated early intervention from two sources, a recent Cochrane Collaboration review and a mapping of European early intervention studies in autism published since 2002. The data extracted focused on methods for describing parent adherence, that is, how and to what extent parents carry out the strategies taught them by therapists. Less than half of the 32 studies reviewed included any measure of parent adherence. Only seven included a direct assessment method. The challenges of developing pan-European early intervention evaluation studies are discussed, including choice of intervention model and of important outcomes, the need for translation of measurement tools and achievement of joint training to reliability of assessors. Measurement of parent–child interaction style and of adherence to strategies taught need further study.
Introduction

This is an exciting time in early autism research. A wide number of scientific methodologies are now being applied to answer fundamental questions about autism, including studying special infant populations such as younger siblings of children with autism; novel neurophysiological and neuroimaging techniques; and development and testing of screening instruments and interventions. Research groups across Europe, brought together by a European Co-operation in Science and Technology (COST) Action ‘Enhancing the Scientific Study of Early Autism’ (ESSEA),1 have been sharing information and ideas about research on preschool children with autism (for a description see Bolte et al. 2013; Garcia-Primo et al. 2014). The aim is to enhance synergy between these strands of basic and applied research, so as to enable developments in clinical practice and policy informed by a rigorous evidence base. The group thereby hopes to contribute to significant improvement of quality of life for children with autism and their families. This paper focuses on one of the Action’s work group topics, testing early intervention approaches in autism through rigorous controlled trials. The group has engaged in a number of collaborative endeavours necessary to enable future European multi-site trials. We consider some examples of activities of the group and focus on one in particular: a review of adherence measurement in parent-mediated intervention studies and a consideration of best practice in this aspect of trial management.

Early intervention: the quality of the evidence

The number of well-designed evaluation studies being published has burgeoned recently. For example, a Cochrane Collaboration review of parent-mediated early intervention trials published in 2002 found two randomized controlled trials (RCTs), whereas an update in 2013 reviewed 17 (Diggle & McConachie 2002; Oono et al. 2013). Magiati and colleagues (2012) identified 15 meta-analyses and/or reviews published in peer-reviewed journals between 2005 and 2012 concerning early comprehensive behaviourally based intervention.

However, most (perhaps all) reviews comment on the mixed quality of the evidence. In the case of RCTs and quasi-RCTs the common flaws include small numbers of participants, risk of bias from attrition and selective reporting, and such varied outcome measures that interpretation of findings is difficult. This has implications for policy and practice; for example, the issues concerning interpretation of the evidence limited the conclusions of the UK National Institute for Health and Care Excellence published guidance on management of autism in children and young people (CG170; 2013) and of similar guidelines across Europe (e.g. for Spain, Fuentes-Biggi et al. 2006; for Italy, ISS 2011).

Activities of the COST ESSEA work group on intervention

The difficulties in conducting rigorous controlled trials determined the agenda for the early intervention work group. The eventual goal would be to facilitate multi-site trials in order to enable recruitment of substantial samples and provide high-quality evidence of effective intervention, which requires detailed groundwork. There are significant obstacles including national and regional differences in assessment tools available, diagnostic practices, quality and quantity of standard treatment and services for young children, and of course language barriers.

The first task was to map published studies since 2002 carried out in Europe. An updated summary is held on the COST ESSEA website.2 The mapping exercise indicated that around half of the studies had evaluated interventions that have a focus on reciprocity between adult (parent/teacher/therapist) and child, including strategies to enhance joint attention and reciprocal communication. Therefore the group has paid particular attention to exploring the strengths and weaknesses of approaches to measurement of observed adult–child interaction. These vary widely, tending to have been developed within individual studies, and including both overall ratings (e.g. parent sensitivity) and frequency counts of behaviour (e.g. child initiatives). A conceptual paper on measurement of adult–child interaction is in preparation.

A second piece of work arose from the realization that there was no consistency across studies in the ways used to describe and summarize quantitatively the other treatments and services being accessed by children and families. It is important to know what children have been receiving, as background to interpreting any observed difference in progress between intervention and control groups. This has led to a Europe-wide survey of parents of young children with autism (E. Salomone et al., unpublished). The development of the survey tool has created a model questionnaire that can be used in future studies across Europe.

A third focus has been on the possibility of harmonizing the choice of outcome measures. An initial count in 17 European

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1 http://www.cost-essea.com/

2 http://www.cost-essea.com/wg4.html
studies revealed 83 different tools to measure outcomes, with very variable evidence of sensitivity to change. A detailed consideration of the strengths and weaknesses of such tools has been commissioned in the UK by the National Institute for Health Research3 which will inform the work in 2014. The work group has also considered a number of ways of circumventing issues of language differences by focusing on measurement of clinically relevant change. For example, an expert panel can use all available data from a study site to make a rating for each participant using the Clinical Global Impressions of Improvement (National Institute of Mental Health 1985). Alternatively, different tools can be considered in terms of the numbers of participants showing clinically relevant change and/or reliable change (Jacobson & Truax 1991). In Italy, Muratori and colleagues (2014) have demonstrated the potential of a standard set of tools in charting progress in children receiving a range of local interventions. The various strands of discussion and enquiry will come together in recommendations of an initial core battery of tools to be adopted in future European intervention trials in autism.

Measuring adherence

The final piece of work focuses on the issue of ‘parent adherence’. Treatment fidelity, or adherence to treatment implementation, can be shown to play a key role in interpretation of the findings of intervention studies (McArthur et al. 2012; Mandell et al. 2013). Treatment adherence can have direct effects on outcome, for example because a larger or higher quality ‘dose’ of treatment may relate to larger outcome gains (Rogers & Vismara 2008). Monitoring treatment fidelity can improve reliability of results, help determine whether the theory-based intervention approach is responsible for the observed changes in outcome, and explore what ‘dosage’ of intervention is optimal.

Issues affecting fidelity can be identified at a number of conceptual stages, starting with intervention design, the training of therapists, how they deliver the intervention, and so on (Bellg et al. 2004; Spillane et al. 2007). In the case of young children with autism, the intervention often involves non-professional delivery, i.e. parents trained by therapists. At each stage adherence to the intended content and quantity of the intervention should be monitored: trainer adherence while training therapists; therapist adherence while teaching parents; parent adherence while working with their children. In addition, this last component can be subdivided into parents’ learning of the techniques and strategies of the approach (described as treatment receipt), and their enactment of the approach (i.e. the extent to which they actually carry out the intervention to the intended ‘dosage’).

There are good examples from the literature of steps taken to ensure therapist adherence when early interventions in autism are directly delivered by therapists. For example, Begeer and colleagues (2011) state that ‘a random 10% sample of therapy sessions was videotaped for content review and intervention adherence. Therapists received ongoing clinical supervision and training throughout the study’ (p. 1000). Likewise Landa and colleagues (2011) report that ‘Interventionists were videotaped on average twice during each intervention session and were blind as to whether videotaping was being conducted for purposes of coding children’s behavior or fidelity’ (p. 16).

However, as we will demonstrate, such examples are harder to find in the literature on parent-mediated interventions for autism. We suggest that this is due to differences between therapist-led and parent-mediated intervention. First, it is easier and more appropriate to secure consent from therapists for monitoring of their intervention practice in clinic than it is to do this with parents in a research study. Second, parents may deliver training naturalistically across the day at home, rather than in a specific session. These factors of timing and location, while they are strengths of using a parent-mediated approach, can lead to a reliance on parent report measures of fidelity.

Parent adherence

At the level of parent adherence, the published evidence does suggest that on average parents can be taught effectively to use a range of different intervention strategies with their children who have autism. A number of studies report measures of parent–child interaction (e.g. McConachie et al. 2005; Kasari et al. 2010; Venker et al. 2011; Siller et al. 2013) where the focus is on the quality of the interaction, although such measures may also document parent use of particular strategies. There can be a rather fine distinction between ‘parent–child interaction’ and ‘parent adherence’. For example, Rogers and colleagues (2012) report the use of the ‘Early Start Denver Model Parent Fidelity Tool’ which, despite its title, involves parents in both the intervention and the control groups being asked to ‘play as you typically do at home’, and the measure is then used in analysis to examine whether change in parents’ skills was reflected in change in child skills. Other studies more directly employ parent–child interaction samples to assess change in parent skills at outcome (e.g. McConachie et al. 2005; Oosterling et al. 2010).

However, we do not generally know whether and how often parents actually use the strategies and techniques with their

3 http://www.nets.nihr.ac.uk/projects/hta/112203
child. Reviews of early intervention studies conclude that the time spent and quality of parent-mediated delivery of intervention strategies to their children is typically not reported (Schertz et al. 2012; Oono et al. 2013).

The current report takes the opportunity provided by the COST ESSEA work group activities and the recent Cochrane Collaboration systematic review of RCTs of parent-mediated early intervention in autism spectrum disorder (Oono et al. 2013) to explore how parent adherence has been measured, both in studies within Europe and worldwide. We present in Table 1 a summary of parent adherence in relation to these two sources of studies: the aforementioned systematic review (Oono et al. 2013) with an additional six studies identified since publication (to end September 2013); and the parent-mediated early interventions from the COST ESSEA mapping of published European studies described above, including mixed controlled group designs (searches to end June 2014).

Of the 33 studies represented in Table 1, 19 did not report recording parental adherence in any way. Six studies asked parents to report on hours of delivery of intervention techniques, usually weekly (Remington et al. 2007; Hayward et al. 2009; Dawson et al. 2010; Wong & Kwan 2010; Pajareya & Nopmaneejumrulers 2011; Schertz et al. 2013), and these included joint attention and reciprocity interventions as well as highly structured approaches such as Early Intensive Behavioural Intervention. Two studies included knowledge tests for parents (Nefdt et al. 2010; Reitzel et al. 2013). One joint attention intervention study (Kasari et al. 2010) developed a questionnaire given to parents weekly, to self-report on adherence and how competent they felt. Finally, seven studies using a range of intervention models included researcher coding of how closely parents were carrying out the strategies of the intervention model (Hayward et al. 2009; Nefdt et al. 2010; Fava et al. 2011; Strauss et al. 2012; Welterlin et al. 2012; Casenhiser et al. 2013; Kaiser & Roberts 2013); six of these were from video and one by home observation of the parent teaching the child. Only Casenhiser and colleagues (2013) and Strauss and colleagues (2012) used these data in analysis to demonstrate a link between parent behaviour change and child behaviour change.

In the case of joint attention or reciprocity interventions, direct monitoring by researchers at planned times is inappropriate as the expectation is that parents will implement strategies opportunistically and flexibly, and specific goals may not be set. However, with video recording becoming more ‘mainstream’, parents themselves may be able in future to arrange to record examples of enactment of strategies in the home setting.

The summary indicates that monitoring of parental adherence is relatively rare in autism treatment studies, but also shows that it is possible to measure this critical variable using a number of different methods, particularly for more structured intervention approaches. Even for reciprocity-focused intervention, parents appear able to self-report on times of implementing strategies, and confidence in their own skills. The possible ways of measuring parental adherence should inform design and planning of future studies, including how adherence interacts with other mediating or moderating variables such as child and parent characteristics. The autism intervention literature may benefit from reference to models of fidelity measurement being derived in other healthcare settings (Bellg et al. 2004).

Discussion

Increased and earlier recognition of autism has increased demand for diagnostic services and interventions. Current healthcare systems internationally are very uneven in terms of their expertise and capacity to support families with young children with autism, often leading to marginalization from society where services are lacking. Within those countries with more readily available services for young children with autism, there is a varied history of the intervention models most usually followed by clinical professionals.

For potential future joint research into evaluation of early intervention across Europe, there are many wide-ranging challenges. These include choice of intervention model, choice of important outcomes, the need for translation of tools for measurement, cultural differences in evaluation of appropriate patterns of parent–child interaction, and how to achieve joint training to reliability of measurement in varied languages. We can now add to this list the need to monitor parent adherence in parent-delivered interventions. The need to strengthen the design and reporting of psychological and social interventions through appropriate guidelines is well recognized (Mayo-Wilson et al. 2013).

In relation to treatment fidelity, the summary in this paper has signposted examples of ways to record time and quality of parent implementation of strategies, depending on the philosophy of the intervention model. Unfortunately these measures of adherence have rarely been related directly to outcomes, nor are they reported in sufficient detail for an accurate evaluation of their methodological quality. Moreover, so few studies report on parent treatment fidelity we cannot yet begin to address more detailed questions of interest, such as whether parent self-report of confidence or tests of knowledge of intervention strategies are adequate proxies for direct assessment of use of those strategies in real life.
Table 1. Early intervention studies, with notes on measurement of parent adherence

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Method and intervention</th>
<th>Adherence measures</th>
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<tbody>
<tr>
<td>Aldred et al. 2004</td>
<td>RCT: social communication intervention. Parent training vs. TAU</td>
<td>Parents were asked to spend 30 min daily alone with their child to practise strategies.</td>
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<td></td>
<td></td>
<td>No measure of parent adherence</td>
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<tr>
<td>Carter et al. 2011</td>
<td>RCT: group parent training using Hanen ‘More Than Words’ programme. Parent training vs. TAU</td>
<td>Parents were asked to spend at least 3 h per day interacting with their child.</td>
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<td></td>
<td></td>
<td>Video scored for fidelity of implementation of techniques (7 items)</td>
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<tr>
<td>Casenhiser et al. 2013</td>
<td>RCT: intervention based on Developmental Individualized Relationships (DIR) model. The programme aims to improve children’s social interaction and communication abilities. Parent training vs. TAU</td>
<td>Number of hours of parent-reported use of techniques</td>
</tr>
<tr>
<td>Dawson et al. 2010</td>
<td>RCT: Early Start Denver Model, a developmental, relationship-based intervention which also includes behavioural techniques. Parent and therapist delivery vs. TAU</td>
<td></td>
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<tr>
<td>Drew et al. 2002</td>
<td>RCT: social communication intervention. Parent training via home visits vs. TAU</td>
<td>Therapist and parent set activities for coming 6-week period with time per activity, but no adherence recorded</td>
</tr>
<tr>
<td>Fava et al. 2011</td>
<td>CT: Early intensive behavioural intervention, therapist- and parent-delivered, including incidental teaching and natural environment teaching vs. eclectic intervention</td>
<td>Treatment fidelity was rated by two independent raters based on video sessions of parents working with their child. Raters used a checklist from Hayward and colleagues (2009) which specifies treatment skills and applications in four domains: data collection (3 items), facilitated play (8 items), discrete trial teaching with mastered skills (11 items), and discrimination training and introduction of new teaching objectives and new programmes (5 items)</td>
</tr>
<tr>
<td>Freitag et al. 2012</td>
<td>Pilot: Frankfurt Early Intervention Program (comparison group data collection in process)</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Green et al. 2010</td>
<td>RCT: social communication and reciprocity intervention. Parent training vs. TAU</td>
<td>Families were also asked to do 30 min of daily home practice. No measure of parent adherence taken</td>
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<tr>
<td>Hayward et al. 2009</td>
<td>CT: clinic-based early intensive behavioural intervention (EIBI) vs. home (parent) EIBI</td>
<td>Sample of videotapes of 15 min standardized protocol assessed by independent practitioner Number of treatment hours per week for each child was measured by recording the start and end times of tutored sessions, parent sessions, shadowed time in school, team meetings and/or workshops</td>
</tr>
<tr>
<td>Jocelyn et al. 1998</td>
<td>RCT: informational intervention for parents and daycare staff vs. daycare attendance</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Kaiser and Roberts 2013</td>
<td>RCT: enhanced milieu teaching (EMT) by parents and teachers vs. by teachers alone</td>
<td>Parents’ use of EMT strategies was coded during home visits where parents conducted trained and untrained play activities with their child, by an observer using the Milieu Teaching Project KidTalk Code. It has 4 variables: % child utterances to which parent responded; % parent utterances that contained a child language target; % child utterances which parent expanded; % prompting episodes that were delivered in response to a child request</td>
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<tr>
<td>Kasari et al. 2010</td>
<td>RCT: Joint attention intervention vs. TAU</td>
<td>Parents report 6 items on adherence and competence at each session</td>
</tr>
<tr>
<td>McConachie et al. 2005</td>
<td>CT: group parent training using Hanen ‘More Than Words’ programme. Parent training vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>McConkey et al. 2010</td>
<td>CT: parent training via therapist home visits using Treatment and Education of Autistic and related Communication handicapped Children (TEACCH), Hanen and Picture Exchange Communication System vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Nefdt et al. 2010</td>
<td>RCT: self-training DVD and manual for pivotal response treatment to teach first words to children vs. TAU</td>
<td>Tests within training. Videos scored by researchers for fidelity of implementation techniques and parent confidence</td>
</tr>
<tr>
<td>Oosterling et al. 2010</td>
<td>Quasi-RCT: social communication intervention by home-based parent training vs. TAU</td>
<td>No measure of parent adherence</td>
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</table>
A further important challenge for early intervention research is to begin to identify parent or family characteristics that may link to ability to implement the intervention, so that parents who are likely to struggle can have additional support. In addition to factors such as accessibility, number of other children and lack of parent education, such characteristics may include whether parents have elements of the Broader Autism Phenotype, likely to reduce flexibility of response (J. Parr et al., unpublished), and conversely parental insightfulness which has been shown to enhance ability to deliver intervention (Siller et al., 2013). There may also be cultural and national differences in parenting which have an impact on intervention delivery. Individualizing approaches to intervention is an important goal for early intervention practitioners.

Future studies need to incorporate multiple measures of fidelity in order to establish which provide an appropriate balance of participant burden against accuracy. In developing these measures the parent-mediated intervention literature can draw on studies of therapist-led intervention for models. This process of monitoring all steps in fidelity adds further complexity to the study of early autism intervention; large numbers of participants are required in order to be able to tease out multiple interacting

Table 1. Continued

<table>
<thead>
<tr>
<th>Identifier</th>
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<th>Adherence measures</th>
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<tbody>
<tr>
<td>Pajareya and Nopmaneejumruslers 2011</td>
<td>RCT: parent training in Developmental Individualized Relationships (DIR) model vs. TAU</td>
<td>Number of hours of intervention delivered reported by parents in a weekly log</td>
</tr>
<tr>
<td>Reitzel et al. 2013</td>
<td>RCT: Functional Behaviour Skills Training groups for children with parent training vs. TAU</td>
<td>Questionnaire to test parent knowledge of applied behaviour analysis</td>
</tr>
<tr>
<td>Remington et al. 2007</td>
<td>CT: therapist- and parent-delivered early intensive behavioural intervention vs. TAU</td>
<td>Parent report estimate of hours per week of therapy</td>
</tr>
<tr>
<td>Rickards et al. 2007</td>
<td>RCT: weekly home-based advice and training to parents by staff member from centre-based programme attended by child vs. centre-based programme only</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Roberts et al. 2011</td>
<td>RCT: home-based programme with parent training in behaviour management, functional communication skills, extending play skills etc., vs. centre-based programme vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Rogers et al. 2012</td>
<td>RCT: low-intensity Early Start Denver Model, parent training vs. TAU</td>
<td>Parent adherence not measured (note that ESDM Parent Fidelity Tool utilized as a measure of outcome and mediation)</td>
</tr>
<tr>
<td>Salt et al. 2002</td>
<td>CT: social-developmental approach, centre-based group attended by child with additional parent training vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Schertz et al. 2013</td>
<td>RCT: joint attention mediated learning, home-based training of parents vs. TAU</td>
<td>Parent recorded log of activities with child, and time spent</td>
</tr>
<tr>
<td>Siller et al. 2013</td>
<td>RCT: Focused Playtime intervention, parent training vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Silva et al. 2009</td>
<td>RCT: parents trained in qigong massage vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Smith et al. 2000</td>
<td>RCT: early intensive behavioural intervention delivered by therapists vs. by parents</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Strauss et al. 2012</td>
<td>CT: early intensive behavioural intervention, therapist- and parent-delivered, including incidental teaching and natural environment teaching vs. eclectic intervention</td>
<td>Parent adherence measured by two independent ratings of parent therapy filmed at home (see Fava et al., above) Amount and difficulty of behaviour targets recorded</td>
</tr>
<tr>
<td>Tonge et al. 2006</td>
<td>RCT: group parent training in behaviour management vs. group parent education vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Venker et al. 2011</td>
<td>RCT: group parent training using shortened Hanen 'More Than Words' programme, Parent training vs. TAU</td>
<td>No measure of parent adherence</td>
</tr>
<tr>
<td>Welterlin et al. 2012</td>
<td>RCT: TEACCH intervention, parent training vs. TAU</td>
<td>Monthly videotaping of 5 min of parents teaching their child at home with materials provided. Percentage of 10-s intervals that parent and child engaged in targeted behaviours. Parent prompts and set-up behaviour coded</td>
</tr>
<tr>
<td>Wong and Kwan 2010</td>
<td>RCT: social communication intervention, parent training vs. TAU</td>
<td>Parent daily record of training activities</td>
</tr>
<tr>
<td>Zachor and Itzchak 2010</td>
<td>CT: therapist early intensive behavioural intervention with parent training vs. professional eclectic plus parent involvement in the home</td>
<td>No measure of parent adherence</td>
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RCT, randomized controlled trial; CT, controlled trial; TAU, treatment/services as usual.
effects. This requirement therefore validates the work of the COST ESSEA network in building capacity for international multi-site trials across European research and clinical sites.

The ESSEA COST Action is enabling European clinical scientists to identify some of the aspects of intervention approaches that have delivered a promising evidence-base. The intention is that this groundwork will lead on to the conduct of trials of intervention programmes across different countries to enhance the power of the evidence base, and also to explore unique and common factors. In the longer term, such a European network might emulate the Autism Treatment Network\(^4\) which includes 17 children’s hospitals and academic medical centres in the USA and Canada, with core funding support from Autism Speaks. It aims to improve health and healthcare for children and adolescents with autism spectrum disorders through research and evidence-based practice. The existence of the network and the large pool of children and families receiving services facilitates multi-site trials, with external research grants including from the US Federal Health Resources and Services Administration. Given the importance of testing the effectiveness of current and emerging treatments for young children with autism, and the need to demonstrate that these can be delivered in communities across Europe, there is a need to identify pan-European funding mechanisms to undertake this work, even in the current financial climate.

**Key messages**

- A number of research groups are active in evaluation of early intervention in autism.
- The predominant models are early intensive behavioural intervention, and reciprocity-focused intervention often involving parents.
- A European network is working towards enhancement of methods for the scientific study of intervention, including how to measure usual services received, and parent-child interaction.
- A review of studies revealed limited methods for measurement of parent adherence to the strategies taught by therapists.
- Multi-site trials of early intervention in autism across Europe are possible, but with many methodological challenges to be solved.


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