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

Helen McConachie, PhD

Professor of Child Clinical Psychology

Institute of Health and Society, Newcastle University

Sir James Spence Institute 3rd floor, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Tel: 0191 282 1396

h.r.mcconachie@ncl.ac.uk

Sue Fletcher-Watson, PhD

Chancellor's Fellow

School of Education, University of Edinburgh

Sue.fletcher-watson@ed.ac.uk

And

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Abstract

Background

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 multisite randomised controlled trials of early intervention, with a specific focus on the need to measure treatment adherence where parents deliver therapy.

Methods

The paper includes a review of randomised 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.

Results

Less than half of the 32 studies reviewed included any measure of parent adherence. Only seven included a direct assessment method.

Conclusions

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.

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.

Multisite trials of early intervention in autism across Europe are possible, but with many methodological challenges to be solved.

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

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 COST Action 'Enhancing the Scientific Study of Early Autism'[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 workgroup 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 2003 found 2 randomised controlled trials (RCTs), whereas an update in 2013 reviewed 17 (Diggle, McConachie & Randle 2003; Oono, Honey & McConachie 2013). Magiati, Tay & Howlin (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 workgroup 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

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

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 initiations). A conceptual paper on measurement of adult-child interaction is in preparation.

A second piece of work arose from the realisation that there was no consistency across studies in the ways used to describe and summarise 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 (Salomone et al, submitted for publication). 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 harmonising the *choice of outcome measures*. An initial count in 17 European 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 Research[3] 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 and Truax 1991). In Italy, Muratori et al (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.

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 (Mandell et al, 2013; McArthur, Riosa & Preyde 2012). 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

[2] http://www.cost-essea.com/wg4.html
[3] http://www.nets.nihr.ac.uk/projects/hta/112203

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 ASD, 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 sub-divided 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 ASD 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. Kasari et al 2010; McConachie et al 2005; Siller, Hutman & Sigman 2012; Venker et al 2011) where the focus is on the quality of the interaction, though 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 2005; Oosterling 2010)

However, we do not generally know whether and how often parents actually use the strategies and techniques with their 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 (Oono, Honey & McConachie 2013; Schertz et al 2012).

The current report takes the opportunity provided by the COST ESSEA workgroup activities and the recent Cochrane Collaboration systematic review of RCTs of parent-mediated early intervention in ASD (Oono, Honey & McConachie 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, Honey & McConachie 2013) with an additional 6 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).

(insert Table 1 about here)

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 (Dawson et al 2010; Hayward et al 2009; Pajareya & Nopmaneejumruslers 2011; Remington et al 2007; Schertz et al 2013; Wong & Kwan 2010) 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 2009; 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 (Casenhiser et al 2011; Fava et al 2011; Hayward et al 2009; Kaiser et al 2013; Nefdt et al 2009; Strauss et al 2012; Welterlin et al 2012); six of these were from video and one by home observation of the parent teaching the child. Only Casenhiser et al (2011) and Strauss et al (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 since 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 health care systems internationally are very uneven in terms of their expertise and capacity to support families with young children with autism, often leading to marginalisation 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 recognised (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.

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 (Parr et al 2014), and conversely parental insightfulness which has been shown to enhance ability to deliver intervention (Siller, Hutman & Sigman 2012). There may also be cultural and national differences in parenting which have an impact on intervention delivery. Individualising 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 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 US 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.

[4] http://www.autismspeaks.org/science/autism-treatment-network

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Table 1 Early intervention studies, with notes on measurement of parent adherence.

Identifier	Method and Intervention	Adherence measures
Aldred 2004	RCT: social communication intervention. Parent training vs TAU	Parents were asked to spend 30 minutes daily alone with their child at home to practise strategies. No measure of parent adherence.
Carter 2011	RCT: group parent training using Hanen 'More Than Words' programme. Parent training vs TAU.	No measure of parent adherence.
Casenhiser 2011	RCT: intervention based on Developmental Individualised Relationships (DIR) model. The MEHRIT programme aims to improve children's social interaction and communication abilities. Parent training vs TAU.	Parents were asked to spend at least 3 hours per day interacting with their child. Video scored for fidelity of implementation of techniques (7 items)
Dawson 2010	RCT: Early Start Denver Model, a developmental, relationship-based intervention which also includes behavioural techniques. Parent and therapist delivery vs TAU.	Number of hours of parent-reported use of techniques.
Drew 2002	RCT: social communication intervention. Parent training via home visits vs TAU	Therapist and parent set activities for coming 6 week period with time per activity, but no adherence recorded.
Fava 2011	CT: Early intensive behavioural intervention, therapist- and parent-delivered, including incidental teaching and natural environment teaching vs eclectic intervention.	Treatment fidelity was rated by two independent raters based on video sessions of parents working with their child. Raters used a checklist from Hayward et al. (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 programs (5 items).
Freitag 2012	Pilot: Frankfurt Early Intervention Program (comparison group data collection in process)	No measure of parent adherence
Green 2010	RCT: social communication and reciprocity intervention. Parent-training vs TAU	Families were also asked to do 30 min of daily home practice. No measure of parent adherence taken
Hayward 2009	CT: clinic-based early intensive behavioural intervention (EIBI) vs. home (parent) EIBI	Sample of videotapes of 15 minutes standardised 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.
Jocelyn 1998	RCT: informational intervention for parents and daycare staff vs daycare attendance.	No measure of parent adherence.
Kaiser 2013	RCT: enhanced milieu teaching (EMT) by parents and teachers vs by teachers alone.	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.
Kasari 2010	RCT: Joint attention intervention vs. TAU	Parents report 6 items on adherence and competence at each session
McConachie 2005	CT: group parent training using Hanen 'More Than Words' programme. Parent training vs TAU.	No measure of parent adherence.
McConkey 2010	CT: parent-training via therapist home visits using TEACCH, Hanen and PECS vs TAU	No measure of parent adherence.
Nefdt 2009	RCT: self-training DVD and manual for pivotal response treatment to teach first words to children vs TAU.	Tests within training. Videos scored by researchers for fidelity of implementation techniques and parent confidence
Oosterling 2010	quasiRCT: social communication intervention by home-based parent training vs TAU	No measure of parent adherence.
Pajareya 2011	RCT: parent training in Developmental Individualised Relationships (DIR) model vs TAU	Number of hours of intervention delivered reported by parents in a weekly log
Reitzel 2013	RCT: Functional Behavior Skills Training groups for children with parent training vs TAU	Questionnaire to test parent knowledge of applied behaviour analysis
Remington 2007	CT: therapist- and parent-delivered early intensive behavioural intervention vs TAU	Parent report estimate of hours per week of therapy
Rickards 2007	RCT: weekly home-based advice and training to parents by staff member from centre-based programme attended by child vs centre-based programme only	No measure of parent adherence.
Roberts 2011	RCT: home based programme with parent training in behaviour management, functional communication skills, extending play skills etc, vs centre-based programme vs TAU.	No measure of parent adherence.
Rogers 2012	RCT: low intensity Early Start Denver Model, parent training vs TAU.	Parent adherence not measured (nb. ESDM Parent Fidelity Tool utilised as a measure of outcome and mediation)
Salt 2002	CT: social-developmental approach, centre-based group attended by child with additional parent training vs TAU	No measure of parent adherence
Schertz 2013	RCT: joint attention mediated learning, home based training of parents vs TAU	Parent recorded log of activities with child, and time spent

Siller 2013	RCT: Focused Playtime intervention, parent training vs TAU.	No measure of parent adherence
Silva 2009	RCT: parents trained in qigong massage vs TAU.	No measure of parent adherence
Smith 2000	RCT: early intensive behavioural intervention delivered by therapists vs by parents	No measure of parent adherence
Strauss 2012	CT: early intensive behavioural intervention, therapist- and parent-delivered, including incidental teaching and natural environment teaching vs. eclectic intervention	Parent adherence measured by two independent ratings of parent therapy filmed at home (see Fava 2011 above). Amount and difficulty of behaviour targets recorded.
Tonge 2006	RCT: group parent training in behaviour management vs group parent education vs TAU	No measure of parent adherence
Venker 2011	RCT: group parent training using shortened Hanen 'More Than Words' programme. Parent training vs TAU.	No measure of parent adherence
Welterlin 2012	RCT: TEACCH (treatment of autistic and related communication handicapped children) intervention, parent training vs TAU	Monthly videotaping of 5 minutes of parents teaching their child at home with materials provided. Percentage of 10 second intervals that parent and child engaged in targeted behaviours. Parent prompts and set-up behaviour coded.
Wong 2010	RCT: social communication intervention, parent training vs TAU	Parent daily record of training activities
Zachor 2010	CT: therapist early intensive behavioural intervention with parent training vs. professional eclectic plus parent involvement in the home	No measure of parent adherence

RCT: randomised controlled trial; CT: controlled trial; TAU: treatment/services as usual