THE PAEDIATRIC AUTISM COMMUNICATION TRIAL - GENERALISED (PACT-G)

1. GENERAL INFORMATION

ISRCTN: 25378536
NIHR REFERENCE: 13/119/18

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Mental Health Research Network (MHRN)
Trial adopted on the network March 2015

PACT will be conducted in accordance with the principles of GCP and applicable UK regulatory requirements

2. PROTOCOL AMENDMENTS

The following changes have been made to the protocol.

Old Version	*New version*	*Date*	*Amendment*
1.0	**2.0**	**06.10.2016**	**Addition of parent questionnaires in sections 8.2 and 8.3**
2.0	**3.0**	**18.11.2016**	• **Finalise list of assessments in section 8.2 and add schedule table in 8.3 Add safeguarding to exclusion criteria** • **Update score on SCQ inclusion** • **Update data collection and CTU information** • **Add exclusion criterion for non-agreement by schools**

3. TRIAL SUMMARY

Background: The evidence base for early intervention in autism shows that behaviours proximal to the intervention delivered (e.g. dyadic interaction measures) are amenable to change, but it has been difficult to generalise treatment gains successfully acquired from one context into another, and no studies to date have demonstrated improvement in general autism symptom severity (difficulty with the generalisation of acquired skills is a key problem in autism).
Aim: This proposal tests an intervention designed systematically to promote generalisation of previously demonstrated clinic-assessed treatment gains into home and school contexts. It includes a detailed mediation analysis building on our previous work and a mechanism study that will enable for the first time a detailed approach to understanding the difficulties of generalising down a known mediation pathway into other contexts.
Hypotheses: 1) The intervention will show the added efficacy and cost-effectiveness of preschool and school-age autism outcomes in home, school and research settings compared to treatment as usual; 2) There will be an increase in the generalisation of acquired communication across contexts and persons, shown by mediation and the mechanistic study.
Design: Three site two parallel group randomised controlled trial of the experimental treatment plus treatment as usual (TAU) versus TAU alone. Initial pilot first stage with pre-specified progression criteria.
Population: Children 2-11 years meeting criteria for core autism on gold-standard measures.
Interventions: The experimental intervention builds on our clinic-based MRC Preschool Autism Communication Treatment model (PACT), delivered with the primary caregiver using methods that gave maximal intervention effect on child social communication, plus an additional series of targeted theory and evidence based strategies designed to enhance the generalisation of this effect into naturalistic home and education contexts (details below). The control intervention will be treatment as usual.
Primary outcome: Autism symptom outcome, researcher assessed in standardised setting.
Secondary outcomes: Autism symptoms, child interaction with parent or teacher, language and reported functional outcomes in home and school settings. Outcomes measured at baseline and 11 month endpoint in all settings with interim interaction measurements (6 months and 8 months) to test mediation.
Sample: 244 (122 intervention/122 TAU; 82/site).
Primary Analysis will test for between-group change in primary outcome using analysis of covariance plus planned subgroup analysis by age-group stratifier and test of moderation.

Mechanism analysis will use regression models to test for mediation of parent-child interaction on primary outcome.
Duration: 42 months, with 6 month start-up, 6 months pilot stage with progression criteria, 24 months for the main trial, and 6 months analysis and write up. 244 cases will be recruited over months 9-26 (4.8/month/site). This is very feasible given that our previous PACT trial with the same inclusion criteria recruited 2.6/month, and recruitment here will be from three times the population pool due to expanded age criteria (<15% of available cases during this period from population estimates).

4. BACKGROUND INFORMATION

The Paediatric Autism Communication Trial – Generalised (PACT-G) builds on the work of Pre-school Autism Communication Trial (PACT) conducted in Manchester, London and North East England between 2006 and 2009. [1]

4.1 Existing research

Intervention research in autism spectrum disorder (hereafter 'autism') has recently accelerated, with studies across a range of interventions considered in recent NICE guidance,[4] Cochrane[9] and other reviews.[11,13] The pattern of findings across a number of interventions is for reproducible moderate to good effects on targeted proximal outcomes such as improvement in interaction and communication in the treatment context[1,10] but weaker evidence for generalisation of treatment effect to broader symptom change and functional outcome.[11] The problem of generalising from 'proximal' intervention effects to wider symptom and functional change is a key current challenge for autism treatment research.[13,14]

4.2 Theoretical background

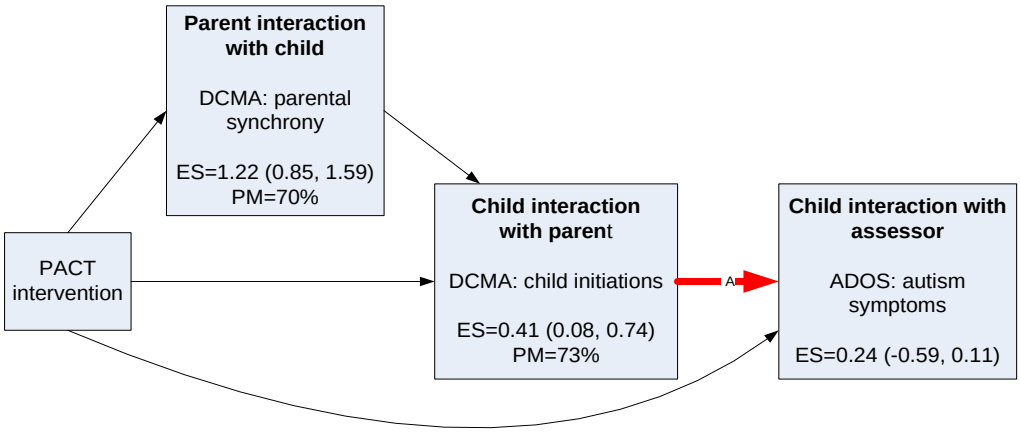
The capacity to generalise acquired skills flexibly across contexts is a central feature of successful developmental learning but a major problem for individuals with autism.[16] Typical development, for instance of language or social skills, depends on children being able to generalise skills acquired in one setting (and with one communicative partner) for use in another (and with other partners). There are a number of theories as to why children with autism should find this so difficult, ranging from their learning style,[17] lack of predictive information coding,[18] probabilistic thinking[19] or weak neural connectivity.[20] However, in practice, from the behavioural/psychological treatment literature there are well-established strategies for enhancing the generalisation of acquired skills.[16,21] *Parent mediated learning*, providing the same dyadic cues for the child across different contexts, is one plausible approach to helping overcome the generalisation difficulties in autism,[22] and *Naturalistic learning,* in which the learning takes place within the functional context in which the skills are actually needed, provides another important approach. Working with children in their natural environments is now highlighted as best practice for early intervention.[23] PACT-G systematically builds on this background and on analysis from our previous trial (described below), by incorporating parent- and teaching staff- mediated intervention strategies within the naturalistic learning contexts of home and education into the PACT intervention model. These additional, evidenced-based, strategies are designed to improve generalisation of the proximal treatment effects demonstrated in our original study to wider symptom change and functional impact in other environments.

4.3 Evidence from the PACT trial

The PACT therapy is a parent-mediated social communication intervention tested in the most substantial trial yet undertaken in the autism field,[1] and has been subsequently subjected to

detailed mediation analysis of treatment process.[24 and supplementary information] The intervention was mainly delivered in clinic, although parents were asked to undertake practice at home. Compared to treatment as usual (TAU), PACT showed a rapid and substantial impact on the targeted immediate outcome of parental communication style (enhanced parental communicative synchrony with the child) (ES 1.22 (95% CI 0.85,1.59) at 13 month endpoint and 1.44 at 6 months). This change in parental synchrony strongly mediated (>70%) a substantial improvement in the child's communication initiations with the parent (ES 0.41 (0.08, 0.74) at 13 months, 0.5 at 6 months). Treatment effect on autism symptoms (measured within researcher-child interaction) was attenuated (ES 0.24 (-0.59, 0.11)) at endpoint, but analysis showed that the endpoint symptom change that did occur was strongly mediated (73%) by the enhanced child communication initiation with parent at midpoint (Figure 1).[24]

Figure 1: Outcome and mediation in the PACT trial[1,24]



ES: effect size of PACT intervention on that variable; PM: proportion mediated of PACT intervention on next step in the causal pathway; DCMA, Dyadic Communication Measure in Autism; ADOS, Autism Diagnostic Observation Schedule (both measures described below). Red arrow shows where the PACT-G targets generalisation.

These results illustrate the attenuation of treatment effect on generalisation across context (parent-child to researcher-child interaction in different contexts), but also demonstrate a causal chain of mediation influence across these contexts. As such, they reflect both the difficulty but also the possibility for generalisation. Thus, while the symptom outcome change at endpoint in PACT was modest, the change that did occur was strongly mediated by the significant change in child dyadic communication with parent. This suggests that the symptom change itself was meaningful in direction and would be increased if the transmission pathway from child initiation to symptoms could be enhanced.[24] The PACT trial was not able to further test the generalisation of the child's acquired competencies into the everyday environment of home or education using blinded measures. However, non-blinded parent-rating showed highly significant generalised treatment gains in both receptive language (OR 3.4 (1.48 to 7.79)), expressive language (OR 1.63 (0.76 to 3.51)) and social communication (OR 2.49 (1.27 to 4.89)),[1] further suggesting the potential for generalisation of treatment effect into naturalistic contexts.

4.4 Rationale for current study

We saw above that generalisation of child acquired dyadic communication skills in PACT was facilitated by having the same interaction partner across environments but weakened when the interaction partner and context changed. Building on this evidence, in this current trial we test a significantly modified PACT intervention including extensions of the intervention procedure into the naturalistic contexts of home and education setting, aimed at enhancing treatment effects in these generalised contexts and with a range of partners. We

will test the impact of this enhanced intervention in both the home and education settings; and the cumulative impact of this in enhancing overall symptom outcomes.

A further modification is to extend the application of the intervention into the primary school years. Autism intervention studies to date have been largely limited to episodic interventions, usually in pre-school. However, communication skills continue to emerge and develop beyond the pre-school years[7] and social communication skills in the early school age period are strong predictors for later development.[8] The developmental nature of autism thus argues strongly for a developmentally sustained approach to intervention into middle childhood.

The ***mechanism study*** will build on the understanding gained from the design and mediation analysis in the original PACT trial as above[24] by assessing the mediators and outcomes in the different generalisation contexts, and thus provide a unique and innovative opportunity to further understand the processes and facilitation of symptom change in autism.

5. RESEARCH OBJECTIVES:

Objective 1 - Testing the efficacy of the PACT-G intervention
To test whether the extended PACT social communication intervention protocol, using targeted enhancement strategies within home and education settings, improves transmission of treatment effect to:
a) Researcher-assessed autism symptom outcome.
b) Autism symptoms and functional adaptation in home and education settings.
This objective will be tested using blinded measures maximising ability to detect meaningful change (see measures below) and evaluated by analysis at trial endpoint.

Objective 2 - Mechanism analysis to illuminate generalised skill acquisition in autism.
The mechanism analysis will use the experimental trial to illuminate core processes of generalisation of specific acquired competencies in autism across context.
(i) We will build on the mediation analysis from our previous PACT Trial (see above) to test mediation of the generalised treatment effect in home and school.
(ii) We will test how effects in naturalistic contexts may combine to enhance transmission of effect to research-assessed symptoms in a standardised test setting.
We will use the pre-specified measures of mediation, which were successful in our previous MRC PACT trial.

6. RESEARCH DESIGN

Efficacy study: Three-site, two-group, randomised controlled trial of the experimental treatment plus treatment as usual (TAU) compared to TAU alone. Children between the ages of 2 – 11 years with defined autism will be recruited to the trial in the local areas following referral via clinical specialists, education professionals and consented databases. After consent families will be randomised on three sites around the UK to receive either the PACT-G social communication intervention in addition to the treatment as usual (PACT-G) or treatment as usual (TAU) alone**.** Assessments are administered on entry (baseline) to the trial, at the 6 month midpoint and at the 11 month endpoint.

There will be an initial 6-month external pilot stage, with pre-specified progression criteria to the full trial. The pilot will be a feasibility, acceptability and recruitment study on 24 cases (8 at each site) using the full baseline and eligibility assessment battery for all cases and the first phase of the intervention for 12 cases. There will be particular focus on the novel aspects of the intervention and research protocol, including the home-based generalization, education buy-in and implementation***.***

Mechanism study: An embedded mechanistic study to test mediation hypotheses and illuminate the basic science of generalisation impairments in autism.

6.1 Randomisation procedure and methods to minimise bias

Research staff will confirm eligibility and obtain consent. Baseline assessment will be undertaken prior to treatment assignment.

Randomisation will be done through the web-based King's College Clinical Trials Unit randomisation service. Allocation will be by minimisation, controlling for treatment centre and age strata (2-5 years, 6-11 years. Each case will be assigned a participant ID number and treatment allocation emailed separately to the treatment centre therapists.

There will be separate clinical and research leads at each site and separate training and supervision structures. Researchers will be housed separately from staff involved in delivery of the PACT-G intervention.

Mid- and endpoint research interviews and assessments will be conducted so as to avoid inadvertent divulging of information that could infer treatment status. The assessment suite and materials used will be quite different in type and location to that used for the therapy intervention avoiding any familiarity effect for children in the treatment arm. The primary outcome and mediation parameters are coded from videotape, by researchers at the other sites, trained to high levels of reliability and blinded to intervention allocation. A random 10% of assessments will be double rated for reliability by an external blinded expert. All other researcher assessments are blinded; parent and teacher questionnaires/interview measures non-blinded.

All therapy sessions are videotaped. Variability due to therapist effects will be minimised by frequent clinical supervision and checks on continuing therapist fidelity against the treatment manual; a minimum of 5% of randomly selected sessions for each therapist will be formally coded for fidelity over the course of the study by independent clinicians using the model successfully used in PACT.

6.2 Study population*:*

Inclusion criteria:

- Age 2 -11 years
- Meeting criteria for autism on the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2);[26] and Scoring ≥15 (school-aged) and ≥12 (preschool) on the Social Communication Questionnaire (SCQ)Parents with sufficient English to potentially participate in the intervention.

Exclusion criteria:

- Sibling with autism already in the trial ,
- Children ≤12 months non-verbal age equivalent level,
- Epilepsy not controlled by medication,
- Severe hearing or visual impairment in parent or child,
- Current severe parental psychiatric disorder
- Current safeguarding concerns or other family situation that would affect child / family participation in the trial.
- No agreement to participate from child's education setting

7. TRIAL TREATMENTS:

7.1 Treatment Principles

PACT-G therapy is an enhancement of the original clinic-based PACT therapy. This is a 'parent-mediated' therapy in which caregivers are coached, using video-feedback, to interact with their child using evidence-based strategies that facilitate communication development in the child. Optimal interaction with a sensitive and responsive communication partner (such as the parent/caregiver) increases communication and social interaction skills in the child. In the original PACT trial this approach was found to be very effective in increasing the quality of parental communicative responses to the child, which in turn led to increased child-initiated communications with the parent.

PACT-G therapy retains these effective elements but adds new features to aid the generalisation of the child's newly acquired skills into other settings, recognising that such generalisation is a particular problem in autism. PACT-G therapy encourages generalisation of skills by extending the therapy into the home and school settings, by integrating the parental techniques into daily routines and play and by widening the range of adults involved in training to include education staff in addition to parents / carers. The therapy begins with the parent at home then extends into the educational setting. Flexibility in timing is built in to fit with school terms, with an overlap to allow for essential supported joint collaboration with parent and education staff.

PACT-G therapy has also been modified to incorporate recent advances in research, focusing on specific strategies to enhance the child's response to adult-directed shared attention and to develop object interest and play. These are important precursors to the early stages of language development[57,58] and have been shown to moderate treatment response in recent social communication early autism trials.[59] Further modifications allow more individual differentiation so that intervention begins at a point appropriate to the child's initial level of object interest and social engagement.

PACT-G therapy, in common with the original PACT therapy, takes a staged approach, which is based on theoretically informed child developmental progression and strategies for establishing essential foundation skills, such as shared attention. Parents and education staff are helped to recognise and facilitate child motivated play (stage 1), and increase their synchrony and sensitive responding (stage 2) with verbal comments on child action and play. Middle stages (stages 3-4) of PACT-G develop language comprehension and expression through language 'mapping' and modelling, and encourage child communication initiations through the use of anticipation and other eliciting techniques. For children who make the most progress, later stages (stages 5-6) encourage language expansion and conversation. PACT-G therapy is appropriate for pre-school and also primary school age children who have severe autism. Some children are likely to be at the earliest stages of communication development making the early developmental PACT-G stages focusing on shared attention, adapted parent responding and eliciting child communication initiation appropriate. Other children may be verbally fluent making appropriate the later PACT-G stages, which focus on language understanding, expression, language expansions and conversation appropriate.

7.2 Treatment Protocol

The sequence of delivery of the PACT-G intervention is set out visually in figure 2.

***Parent sessions*:** Based on what was found to be most effective in the original PACT trial, parents will receive 12 intervention sessions. Prior to starting the intervention, a home visit is conducted to introduce the intervention to the parents, explore the family context and set expectations. Where feasible the first two sessions are delivered in a clinic, allowing the

parent to learn early strategies in a controlled environment with a set of toys specially selected to facilitate interaction. Subsequent sessions are a mix of home based sessions and Skype/telephone-delivered consultation. This approach will assist generalisation of new skills development in the home setting. Clinical and research experience indicates that these session formats are popular with parents.[34] Each parent session begins with a discussion of progress made since the last session. The parent and therapist then watch a 5-minute video, either a video made by the therapist of the parent and child in play or a parent-made video of a home based routine, such as mealtime. The therapist facilitates the parent to identify actions that lead to child communication and to adopt PACT-G strategies in their interaction with the child. Parents are assisted to set goals for themselves, based on the interaction strategies discussed. They are asked to practice these daily, initially in a half hour 'special time', but eventually during naturalistic opportunities throughout the day.

Education setting sessions: Therapy in the educational setting begins after the parent has commenced therapy, with a start time integrating into the school term schedule. In the education setting PACT-G sessions will be delivered to trained learning support assistants (LSA), who are additional staff with a specific remit to attend to the child's special needs and thus with dedicated individual time in the classroom or nursery. LSAs and other education staff receive an initial training session to introduce them to PACT-G therapy. The education-based intervention then consists of therapist-LSA sessions that mirror the therapist-parent sessions in the home. Videos are made of the LSA and the child and are used to coach the LSA in the use of appropriate PACT-G strategies. The LSA then implements these with the child daily in class time. There are 12 therapist-LSA sessions over 6 months, alternating in-school visits and skype/telephone consultation. PACT-G strategies will be also integrated in a complementary way with other communication strategies that may already be in use in the school.

***Collaboration between parent and educational staff*:** Importantly, the separate therapeutic work with parents and LSAs described above will be supplemented with a schedule of joint parent-LSA meetings to support the work and ensure consistent use of strategies across home and education settings. This will be key to successful generalization. The meetings will use the manualised technique of 'Structured Conversation with Parents' (SCP). Meetings are structured around 'explore', 'focus', 'plan' and 'review' stages, which allow the LSA and parent to share experiences and maximize intervention consistency. SCP is validated and shown to be highly effective in motivating parents and schools.[51,52]

Figure 2: Intervention and assessment timeline

<table>
<tr><td>Month</td><td>0
Baseline</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11
Endpoint</td></tr>
<tr><td colspan="13">Research Setting</td></tr>
<tr><td>Assessment</td><td>BOSCC ADOS</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>BOSCC ADOS</td></tr>
<tr><td colspan="13">Home Setting</td></tr>
<tr><td>Assessment</td><td>BOSCC DCMA</td><td></td><td></td><td></td><td></td><td></td><td>BOSCC DCMA</td><td></td><td></td><td></td><td></td><td>BOSCC DCMA</td></tr>
<tr><td>Intervention with parent</td><td></td><td colspan="6">Initial home visit
12 intervention sessions (a mix of clinic and home based sessions and telephone/skype support sessions)
Monthly SCP sessions in school</td><td colspan="4">SCP sessions continue for the period of the school intervention. The number will vary depending on term times but with a minimum of 3 sessions</td><td></td></tr>
<tr><td colspan="13">Education setting</td></tr>
<tr><td>Assessment</td><td>BOSCC DCMA</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>BOSCC DCMA</td><td></td><td></td><td>BOSCC DCMA</td></tr>
<tr><td>Intervention with education</td><td></td><td></td><td></td><td colspan="5">Initial LSA in-school training visit*
12 intervention sessions (6 school alternating with 6 Skype/telephone support) incorporating monthly SCP meetings with parents**</td><td colspan="2">SCP sessions continue until final assessment</td><td></td></tr>
</table>

*Start of education element accommodates school terms **Structured Conversation with Parents – see text.

7.3 Training and Fidelity of Treatment

Training in the PACT-G therapy will be conducted centrally by the lead speech and language therapists, who will undertake overall co-ordination of the therapy in the trial and will organise quarterly national therapist meetings. Therapists will be regularly supervised by the lead speech and language therapists in each site. All therapy sessions will be videotaped and 5% of randomly selected tapes will be independently rated using the PACT Fidelity Rating Scale at regular intervals across the trial period.

Therapists in the trial will not be treating any TAU patients.

Therapists and research staff will be trained in practices that minimise noncompliance and drop-out. Therapy compliance and receipt of other interventions outside of the protocol will be monitored.

7.4 Treatment as Usual

The control intervention will be treatment as usual (TAU). We have detailed information on TAU in the pre-school population from the group's previous work on the MRC PACT trial and in older children from the PACT 7-11 early school study.[2] Data on services received will be collected.

8. ASSESSMENTS AND PROCEDURES

8.1 Primary outcome

Brief Observation of Social Communication Change (BOSCC) with researcher.[27,28] BOSCC is a researcher-coding of autism symptoms from videotaped child-adult interaction. It addresses the same autism symptom construct as ADOS (which was used in the original PACT trial) but is designed to better detect clinically meaningful symptom change in treatment studies, with codes combining symptom frequency, severity and atypicality on a 16-item, 0-5 scale (overall range 0-80). BOSCC is designed to be a standard treatment outcome measure for the autism field and is currently used in large funded trials in US and EU. It shows high inter-rater agreement[28] and increased sensitivity to treatment change compared to ADOS (BOSCC d=0.64 compared to parallel ADOS d=0.42 in a recent 12 month observational intervention study).[29]

8.2 Other measures

Mullen Scales of Early Learning[36] or British Ability Scales;[37] depending on child age and ability level. These are standard measures of non-verbal early development which enables a developmental level of non-verbal abilities to be ascertained for inclusion criteria and to allow characterisation of the cohort in relation to other autism treatment trials.

Social Communication Questionnaire (SCQ) Standard instruments, to be used for diagnostic inclusion.

Autism Diagnostic Observation Schedule (ADOS-2). The standard autism diagnostic symptom measure with good external validity to long-term outcomes.

Brief Observation of Social Communication Change (BOSCC) with parent and LSA. Coded from video of child-parent play-session in home (baseline, 6 month midpoint, 11

month endpoint) and child-learning support assistant in school (baseline, 8 month interim, 11 month endpoint); measure of intervention effect in naturalistic settings in which intervention took place.

Dyadic Communication Measure for Autism (DCMA) with parent and with LSA. Coded from video of the child-parent play-session at home (baseline, 6 months midpoint, 11 month endpoint) and child-learning support assistant play-session in school (baseline, 8 months interim, 11 month endpoint). This measure includes independent codes of parental communication (synchrony) and child communication (initiations). This measure proved sensitive in the original PACT mediation analysis and will be used in PACT-G to test treatment effect and mediation in home and education settings.

Vineland Adaptive Behavior Scales. Parent and teacher versions (P/T-VABS).[38] The VABS includes domains of communication, daily living skills and socialisation, and has been used in numerous autism studies. It will be a measure of functional gains by the child in the home and education settings.

MacArthur-Bates Communicative Development Inventories (Word and Gestures; Sentences and Grammar); and Receptive and Expressive One-word Picture Vocabulary Test; and Pre-school Language Scale-5. The overall language level measured by these standardised assessments supplements that of the measures of autism-specific communication measured in the BOSCC.

Warwick & Edinburgh Mental-Wellbeing Scale.[33] Parent rated well-being questionnaire recommended by DoH as the preferred measure of mental wellbeing important to incorporate in studies of this kind.

Child and Adolescent Service Use Schedule (CA-SUS). Developed to record service use and adapted to young populations with autism in our PACT and PACT7-11 studies.[1]

Working Alliance Inventory – Short Revised (WAI-SR) Therapeutic Alliance questionnaire; measure of engagement with therapy for parents and learning support assistants in intervention group only; For parents and LSAs, there is a simple rewording of the client and therapist versions of the WAI-SR, which has been validated and is now frequently used. Completed at 2 and 5 months into the intervention.

Family History Interview (FHI). Measure of the Broader Autism Phenotype (BAP) in parents. Completed at midpoint assessment.

Strengths and difficulties questionnaire (SDQ) – Parent and Teacher versions The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) Short Form is a 25-item brief measure of psychological wellbeing in 2-17 year olds. In PACT-G, it will be completed by both parents and teachers.

Tool to Measure Parental Self-efficacy. A 48-item, self-report measure of parenting competence. It is a measure of possible change in parent's confidence in their ability to make a difference to their child's development. Completed at baseline and endpoint assessments.

Epworth Measure of Daytime Sleepiness A self-report questionnaire of how likely someone is to doze off or fall asleep in eight everyday situations, in contrast to feeling just tired. Each item is responded to on a 4 point scale.

Child Health Utility 9D A paediatric measure of health related quality of life. It consists of nine items, each responded to with one of five levels (ranging from no problems to severe problems). The CHU9D is designed to be completed by children aged 7-17. Proxy

completion is also possible for younger/ developmentally disabled children. In PACT-G parents will be asked to complete this questionnaire on behalf of their child.

Repetitive Behaviours Questionnaire – 26 point questionnaire; the RBQ is one of the most commonly used for assessing repetitive behaviours in children with ASD

Demographic, language and service use information – we will collect relevant demographic information and details of languages spoken with the child; as well as information about therapies and services accessed throughout participation in the study

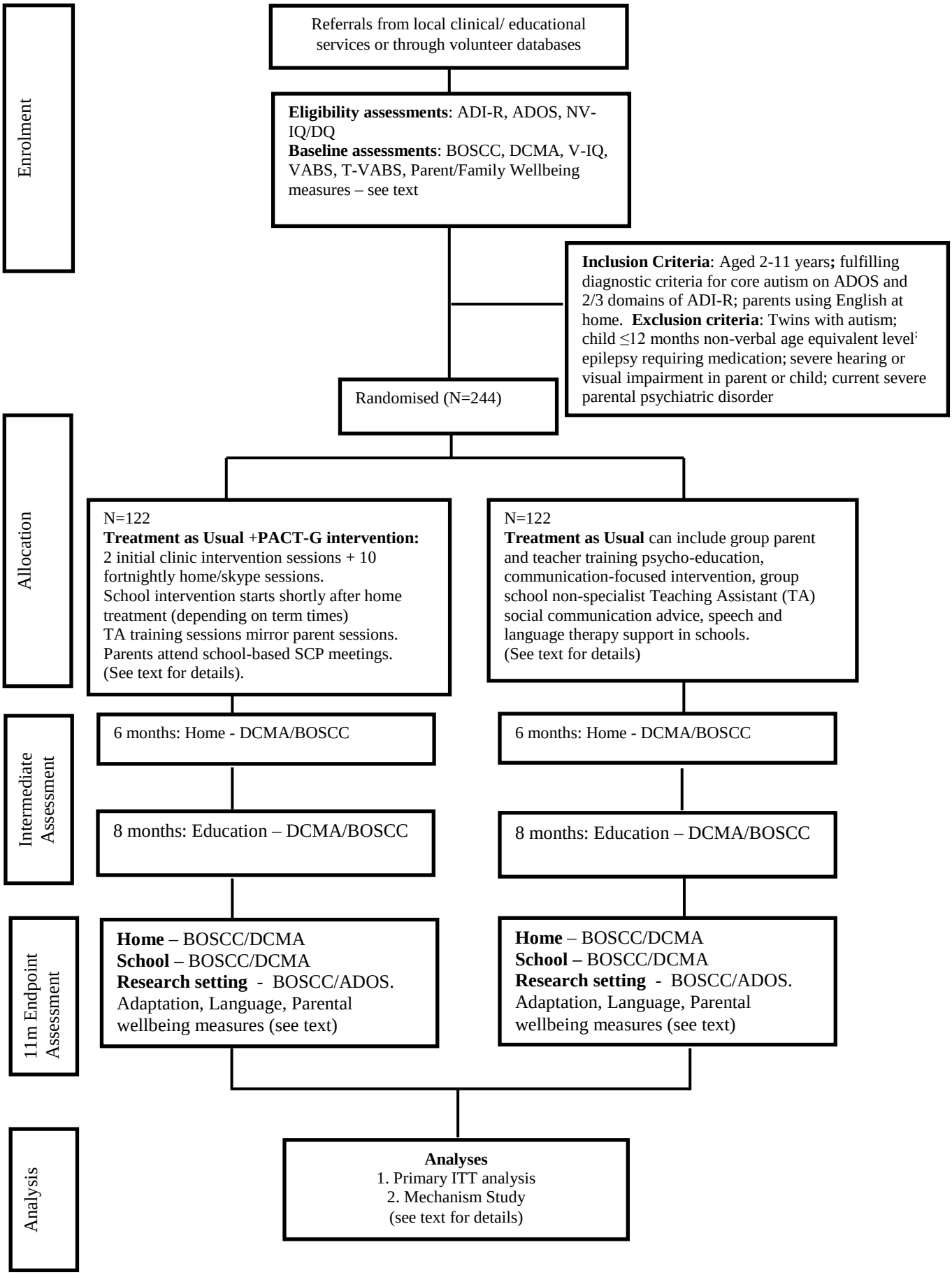
8.3 Schedule of assessments

The table below shows the full schedule of assessments

	Measure
Eligibility	SCQ
	ADOS-2
	Mullen Scales of Early Learning (pre-school children)
	British Ability Scales (school-age children)
Baseline	BOSCC - Researcher
	BOSCC/DCMA - Parent
	BOSCC/DCMA - LSA
	Vineland - Parent Interview
	Vineland - Teacher Survey
	VEPS
	Receptive and Expressive One-Word Picture Vocabulary Test
	Repetitive Behaviour Questionnaire
	Warwick & Edinburgh Mental Wellbeing Scale
	Epworth Measure of Daytime Sleepiness
	MacArthur-Bates Communicative Development Inventories (Word & Gestures; Sentences & Grammar)
	Strengths and Difficulties Questionnaire - Parent
	Strengths and Difficulties Questionnaire - Teacher
	Tool to Measure Parental Self-Efficacy
	Child Health Utility 9D
	Key Information and Demographics
	Clinical Information and Service Use
	School Service Use Form
	Family Language Interview
6-month Home/Parent	BOSCC/DCMA - Parent
	Family History Interview
	Status Form
8-month LSA/School	BOSCC/DCMA - LSA
Endpoint	ADOS-2
	SCQ
	Repetitive Behaviour Questionnaire
	BOSCC - Researcher
	BOSCC/DCMA - Parent
	BOSCC/DCMA - LSA
	Preschool Language Scale-5
	Receptive and Expressive One-Word Picture Vocabulary Test

	Vineland - Teacher Survey
	Vineland - Parent Interview
	Warwick & Edinburgh Mental Wellbeing Scale
	MacArthur-Bates Communicative Development Inventories (Word and Gestures)
	Epworth Daytime Sleepiness Scale
	Strengths and Difficulties Questionnaire - parent
	Strengths and Difficulties Questionnaire - Teacher
	Tool to Measure Parental Self-Efficacy
	Changes to Key Information and Dempgraphics
	School Service Use Form
	CASUS
	Child Health Utility 9D

PACT-G Consort Diagram



9. STATISTICAL ANALYSIS

9.1 Sample Size Calculations

Our PACT trial showed an effect of ES 1.22 (0.85, 1.59) on parental synchrony (DCMA), which mediated 70% of the ES 0.41 (0.08, 0.74) on Child communication, which in turn mediated 72% of the ES 0.24 (0.59, 0.11) on symptom outcome (ADOS). The intervention strategies in PACT-G are specifically targeted to enhance generalisation of the child communication to increase primary outcome effects in home, education and research settings. Therefore we expect the ES for the symptom outcome to be substantially above 0.24 and clinically meaningful (see above). Power was calculated using the sampsi command in Stata, for an analysis using ANOVA with alpha=.05, with pre and post measures correlated .67 (from PACT trial). With 110 cases followed up in each group (70/70 preschool and 40/40 school-age) 80% power is retained for ES=0.28 and 90% power for ES=0.33. Allowing for 10% attrition (compared to 4% in PACT) we propose to recruit 244 families (82/site - 52 pre + 30 school-age). The improved reliability available from using the additional midpoint BOSCC (not available for ADOS due to risk of learning effects from repeat testing) raises the corresponding power to 90 and 97% respectively.

9.2 Analysis Plan

All analyses will be carried out using Stata[32] or MPlus (see http://www.StatModel.com). In accordance with CONSORT guidelines, we will report all participant flow. Descriptive statistics of recruitment, drop-out and completeness of interventions will be provided.

Phase 1 - Efficacy Analysis. The main efficacy analysis will be via intention-to-treat including all participants, with no planned interim analysis for efficacy or futility. Baseline characteristics will be presented by randomised group without formal statistical tests. We will test the primary hypothesis for between-group change in the primary outcome using analysis of covariance with baseline outcome measure, centre, ADOS severity, age-group stratifier and treatment assignment as fixed effects, and apply standard regression diagnostics. The analysis will use statistical techniques for handling missing outcome data under a missing at random assumption and multiple imputation for missing baseline measures. The secondary outcomes will be analysed using an analogous method. Analysis of all treatment effects will be undertaken after 11 month outcome measures are completed. We will test effects in pre-school and school-age children with planned subgroup analysis by age-group stratifier; and test an optimal moderation index[3] including bootstrap for bias-correction from over-fitting to a finite sample.

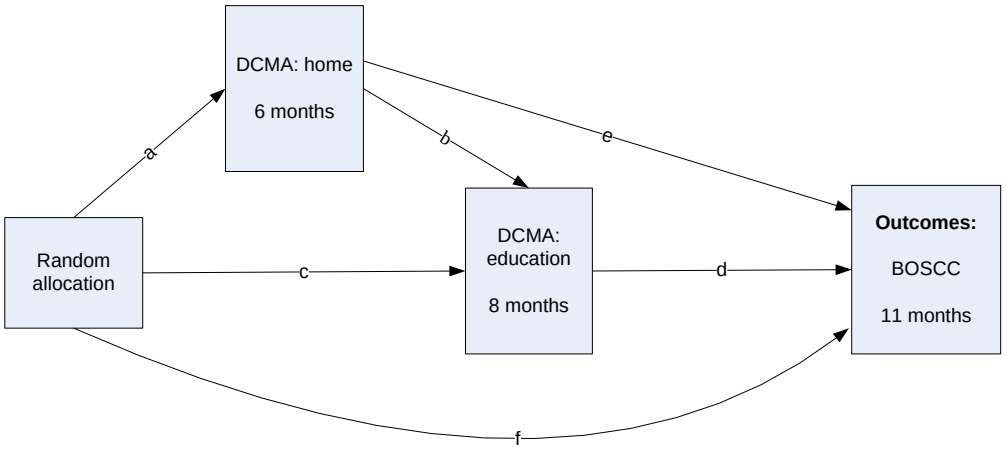
Phase 2 - Mechanisms Evaluation. Mediation analysis[24] gave detailed insight into an attenuated generalization in the original PACT trial across change in person, task and context (as above and Figure 1). In PACT-G we enhance generalisation *into home* by keeping parental dyadic cues constant but increasing functionally relevant interaction contexts; and *into education* by enhancing relevant communication with education staff (LSA). The mechanism study will investigate the mediation process in this model and through that illuminate key basic knowledge about generalisation in autism. The pathways of interest are illustrated in Figure 3. If the efficacy analysis shows significant between group differences in the mediators (DCMA at home (path a) and education setting (path c)), then we will use parametric regression models to:

1. test for mediation of the intervention on BOSCC outcomes at home through DCMA at home (paths a,e,f);
2. test for mediation of the intervention on BOSCC outcomes in education setting through DCMA at education (paths c,d,f);
3. test for mediation of intervention on DMCA in education setting through DCMA at home (paths a,b,c);

4. use structural equation modelling to examine multiple pathways through DCMA at home and education setting to generalisation on the primary outcome of researcher BOSCC (paths a-f)

Since all the measures are continuous, the indirect effects are calculated by multiplying relevant pathways and bootstrapping is used to produce valid standard errors for the indirect effects. All analyses will adjust for baseline measures of the mediators (DCMA), outcome (BOSCC or ADOS) and putative measured confounders, and be tested for moderation by age-group stratifier. Mediation analyses are potentially biased by measurement error in mediators and hidden confounding between mediators and outcomes; we will build on our previous methodological and applied work in this context to include repeated measurement of mediators and outcomes to account for classical measurement error[24] and baseline confounding. We will investigate the sensitivity of the estimates to these problems and that of unmeasured confounding using instrumental variable (IV) methods[6] with baseline covariate by randomization interactions as potential instruments.[6]

Figure 3: Key mediation pathways to be tested in PACT-G mechanism study.



Treatment compliance in the education setting is likely to be more variable than the high levels achieved with parents. We will estimate a complier average causal effect (CACE) estimate using instrumental variable methods, considering the education-setting opt-in as a measure of compliance and randomisation as the instrumental variable.

Phase 3 - Moderation and subgroups: We will test whether the mediation analysis is consistent <u>across</u> the two age-groups by testing for moderation of paths a-f by age-group stratifier (including interaction terms or performing a multiple group analysis in the structural equation model). We will test "*moderated mediation*" on our pathway from intervention to interaction with an unfamiliar assessor, extending our understanding of generalisation processes in autism. The heterogeneity of autism is well-recognised and as such offers numerous potential moderators of treatment effects (e.g. language level, restricted and repetitive behaviour, functional impairment). We will examine an extended list of moderators using bias correction/cross-validation methods (we are currently comparing the performance of alternative penalisation methods using the original PACT data and will apply our findings from this to the current cohort) to identify robust evidence for moderation and for a moderation index, both on the overall effect and also along the steps of the mediation pathway. Due to our proposed sample size, the power of analysis possible here will be unprecedented in autism research (and to our knowledge in other areas of psychological intervention in childhood).

10. TRIAL SUPERVISION

This study will be sponsored by Central Manchester University Hospitals NHS Foundation Trust and subject to normal governance arrangements.

10.1 Trial Steering Committee

We will form a trial steering committee (TSC), which will include an independent chair, parent representatives from the PACT 7-11 cohort and other service user representatives, as well as national organisations such as the National Autistic Society, which has strongly supported the PACT and PACT 7-11 studies from the outset. This steering committee will be consulted on the final design of the follow-up, techniques for ascertainment and the focus for measurement. The TSC shall meet once prior to the commencement of the trial and annually thereafter.

10.2 Data Monitoring and Ethics

There will be an independent data monitoring methods committee (DMEC).

10.3 Project management group

The project management group will be chaired by Professor Green and consist of the Principal Investigators and senior researchers on the trial, the Trial Manager and other invited members as necessary. It will meet at least quarterly, with additional tele or video-conferencing as necessary.

10.4 Adverse events

We will collect information about adverse events; as well as recording adverse events in the standard way, we will include events particularly relevant to this trial, such as significant changes in family or school situation.

11. DATA HANDLING AND RECORD KEEPING

All data in the trial will be anonymised. A central master file will be held by the trial manager at the Room 3.316, University Place, The University of Manchester, Oxford Road, Manchester M13 9PL. This will contain the key linking anonymised trial name to personal details. This eCRF pack will be backed up securely within the web based data entry service of Kings College CTU. All data will be entered into the Kings web based secure MACRO database, which has a full audit trail and appropriate quality control will be carried out during the trial and before the database lock..

12. DATA ACCESS AND QUALITY ASSURANCE

Primary analysis of the data will take place in Kings College, London and the University of Manchester by the trial statisticians, Professor Andrew Pickles and Dr Richard Emsley, and Chief Investigator, Professor Jonathan Green. Other members of the team will also have access to data and will undertake analysis as appropriate and necessary. Any arrangements for other researchers in the general field to have access to the primary data will be negotiated separately and COREC informed.

The data will be stored in the Academic Department of Child Psychiatry, University of Manchester. Paper copies will be stored centrally in secured cabinets. Electronic data will be stored within the Kings College CTU secure data storage facility and on the central computer of the Department of Child & Adolescent Psychiatry, University of Manchester. The custodian will be Professor Jonathan Green, Chief Investigator of the study.

13. PUBLICATION

The results of the research will be targeted for publication in peer-reviewed journals of general and special interest. There will also be a general dissemination programme for families including participants co-ordinated through our collaborators in the National Autistic Society. Individual feedback for participants will be through the regular trial newsletter.

14. FINANCE

NIHR Research funding - £1,699,810.24
DH funding for excess treatment costs - £857,870.00

15. ETHICAL APPROVAL

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