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# BMJ Open

## Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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# Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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## Abstract

Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is the only parent-mediated therapy that has shown a significant and sustained impact on autism symptom reduction. However, the access to such evidence-based therapies for families is limited due to autism centers located in large urban area. Using videoconferencing to deliver PACT training to parent may improve accessibility for families living in underserved areas.

This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12 months period. It will compare PACT with treatment as usual (TAU) with TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 min away from the specialist centres for autism. Primary outcome will be the change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analysis will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

## Article Summary

### Strengths and limitations of this study

- Large multicentre RCT in children with ASD under 3 years old
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved area
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists cannot be blind to the allocation group.

**Keys Words:** Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

**Trial registration:** ClinicalTrials.gov Identifier: NCT04244721

# Introduction

## Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of 1-1.5% that can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months years old [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years have the potential for maximal impact on autism symptom severity[6–8].

Therapies can be delivered by therapists, teachers and parents [9]. For preschool children with ASD, parent-mediated therapies can empower parents to face challenging social interaction with their children [8,10]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication therapy) is the only therapy to have shown a significant short and long-term effect in children aged from 2 to 9 years in a large UK cohort (N=152)[9,11,12]. In PACT, parents are guided by a therapist via video feedback to optimize their interactive behaviours in order to enhance parent-child dyadic interaction, which in turn will impact on child language, communication and autism symptoms (PACT reference) [13]. At 13 months, PACT showed a statistically significant reduction in the severity of symptoms and showed an increase in parental communication synchrony with the child, child communication initiations with parents and for parent-child shared attention [11].The follow-up study demonstrated a reduction in autism symptom severity PACT therapy five years after the PACT intervention [14]. The symptom severity as measured by the Autism diagnostic Observation Schedule version 2 (ADOS-2) was significantly reduced between both groups (Effect size=0.55, 95% CI 0.14 to 0.91, p=0.004)[12]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiatives, which in turn was mediated by improved parent-child synchrony [15].

Availability of PACT therapy is limited; even more so in rural setting or in regions away from specialist centres. Training parents to PACT via videoconferencing conducted by trained therapists may be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to successfully provide parent-mediated therapy in autism by videoconference [16,17]. The team who developed the PACT therapy has a positive experience of parent guidance by videoconferencing (personal communication). Indeed, remote PACT was partly used, during some session, in a recent RCT [18]. However, PACT has never been evaluated when exclusively delivered by videoconference. The barriers and facilitators of videoconferencing therapy are not sufficiently well known, and hence it is also essential to address them properly [19,20].

The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness of PACT therapy delivered to parents by videoconference. A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

The hypothesis is that PACT intervention + TAU (Treatment As Usual) will have a superior efficacy on child autism symptom severity as compared to TAU alone.

## Objectives

Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, in which professionals guide parents via videoconferencing, over a 12-months period, on overall autistic symptoms measured with a standardized measure, the Autism Diagnostic Observation Schedule (ADOS), in children with ASD aged from 18 to 36 months at inclusion, living in underserved area.

Our secondary objectives, at the child level, will be to evaluate the development of socio-communicative interactions in naturalistic environment, language, initiatives in the communication and daily adaptive behaviour. At the parent level, we will evaluate the intervention effects on stress, health and family priorities.

The implementation of the therapy will be evaluated through the adherence of the professionals and of the parents to the PACT, and through parents and professionals' acceptability and feasibility of the PACT sessions.

## Method

### Study design (see figure 1 flow-chart of the study)

Our study is a multicentre, prospective, 2 parallel groups, 1:1 ratio, single blind Randomised controlled trial (RCT) comparing PACT intervention + Treatment As Usual (TAU) to TAU alone. Evaluation is based on a mixed-method approach combining quantitative and qualitative studies [21,22].

A qualitative study will be conducted to capture further experience of the implementation of the intervention and causal pathway of effectiveness or ineffectiveness according to the therapists and the parents.

### Setting

We will run this trial in six academic centres in France. These centres are located in child and adolescent public hospitals. All centres have a unit for ASD diagnosis and assessment and a distinct unit for intervention where therapists have been trained in PACT and can provide PACT via videoconferencing. Children they care for come from a French-speaking population including socioeconomically disadvantaged groups.

### Population

#### *Inclusion criteria*

Children will be included if they meet the following criteria:

- i) aged between 18-36 months old at inclusion
- ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism Diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised) [23–25]. For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will have to be greater or equal to 4. The score on the ADI-R algorithm for toddlers will have to be greater or equal to 11 [26]. The



1  
2  
3 diagnosis will be confirmed by a multidisciplinary team specialised in Autism Spectrum Disorder  
4 diagnostic and assessment based in the academic department of hospital.

5 iii) have a non-verbal age equal or above 12 months on the Mullen Scale of Early learning ( MSEL) [27].

6 iiiii) live more than 40 minutes away from a Center for Resources in Autism (regional center)  
7  
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10 Referent parents will be included if they meet the following criteria:

11 ii) speak French with their children

12 iii) are able to do videoconferencing with therapists from the center (assessed through the conduct of  
13 the Vineland Assessment Behavioral Scale by videoconferencing)  
14  
15

### 16 ***Exclusion criteria***

17 Exclusion criteria will be as follows for the child:

18 i) a twin brother or sister with ASD or a brother or sister having already been included in the study

19 ii) diagnosed with epilepsy requiring medication

20 iii) have a severe hearing or visual impairment

21 iv) an identification of a genetic anomaly which may impact on their ability to participate in the  
22 intervention or on data validity (determined by the principal investigator on a case-by-case basis).  
23  
24

25 Exclusion criteria will be as follows for the referent parents (at least one parent with):

26 i) severe hearing or visual impairment

27 ii) severe psychiatric disorder

28 iii) unstable somatic disorders preventing participation in the intervention

29 iv) lack of internet provision

30 v) not available for regular intervention and follow-up

31 vi) opposition of one parent to the child's participation in the study  
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### 40 **Intervention conducted in the experimental group**

#### 41 ***Eligibility criteria for PACT therapist and adherence***

42 Therapists may include will be speech language pathologists, Occupational therapists, Clinical nurse,  
43 psychologists or child and adolescent psychiatrist, all specialised in autism. The therapists have already  
44 received formal training and supervision in PACT with the team who developed this training [11,28].

45 The lead therapist will organize regular meeting between therapists of all centers, with scoring and  
46 feedback of videotaped therapy session of the study, in order to maintain a high fidelity to the therapy.  
47  
48

#### 49 ***PACT treatment principles***

50 As previously described [18], parents will be trained, via video-feedback, to identify and set up key  
51 strategies facilitating the socio-communicative interactions between their child and themselves.

52 Parent will also be encouraged to use PACT every day outside the training session at least half an hour  
53 per day. The therapy follows a six-staged approach based on child developmental progression and  
54 strategies for setting up fundamental skills for the socio-communicative development as shared  
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3 attention. The 2 first stages aim to increase parent's identification of child focus and interest,  
4 synchrony, responsiveness and sensitivity to the child interest and communication. The third and 4th  
5 stages are targeted towards developing expression and comprehension of the child by commenting  
6 and modelling with a language adapted to the child's one. The child initiative in communication is also  
7 improved through the means of different strategies such as anticipation and routine. The 2 last stages  
8 aim to develop conversation and expansion of language for verbal children. Progression from one stage  
9 to the other depends on predefined criteria.

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12  
13 Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with  
14 the therapist over the 12 months (Green, 2010; Pickles, 2016): 1 hour session every fortnight during 6  
15 months to learn PACT strategies then, 1 hour session per month over the last 6 months to maintain  
16 the capacity of parents to deliver the strategies.

17  
18  
19 Therapist will train only one parent per family and maintain fidelity to the therapy manual. The  
20 "referent parent" will have to be designated before the randomisation of the child. If the referent  
21 become unavailable, the therapy will stop or will continue with the other parent if possible and will be  
22 reported.

### 23 24 25 ***Parent training session with the professional via videoconferencing***

26  
27 Before each session, parent will be asked to send a 10 minute video of an interaction with his/ her  
28 child, to the therapist via a secure cloud link. During the videoconferencing session (as in face to  
29 face), referent parent will begin with a 5 minutes discussion about progress since the last session.  
30 The therapist will then share his/her screen and watch together with the parent the home-based 10  
31 minutes video. They will identify, review and discuss specific clips that demonstrate accomplishment  
32 of therapy goals for each stage of the programme. The therapist's role will be to guide parents to  
33 identify their successful strategies and responses (i.e episodes of engagement and/ or mutual sharing  
34 with their child). Parents will be helped to reflect on their role in enhancing interaction and to  
35 identify new intervention goals.

### 36 37 38 39 40 ***Parent PACT implementation in daily life outside the therapy session***

41  
42 At the end of each session, the therapist will support the parent in setting 2-3 goals, based on the  
43 strategies identified during the session. The therapist will encourage the parents to practice the  
44 strategies for the next session and will discuss opportunities to achieve these goals in daily routine at  
45 home for at least ½ hours per day. Parents will be guided to embed PACT strategies in diverse everyday  
46 routines in different contexts. As therapy progresses, parents will be asked to send 10-minutes home  
47 videos of short daily routines in different contexts.

### 48 49 50 **Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management**

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52  
53 Regardless of group allocation, parents will receive treatment as usual (TAU) consisting in an  
54 information about ASD, its management, and educational support for nursery and preschool  
55 placement. Parents will be referred to any relevant care available in the community (e.g.: Speech  
56 language pathologist (SLP), occupational therapist, educator, behavioural psychologist, psychiatrist).  
57 TAU received during the course of the study will be described in both groups.

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3 Regardless of group allocation, a psychiatrist or a psychologist from each autism centers will provide  
4 two supplementary 45 minutes follow-up consultations conducted by videoconferencing, at 3 and 6  
5 months after inclusion. They will follow an interview guide. Three thematic areas will be systematically  
6 discussed with the parents: ASD information, access to treatment in the community, support for school  
7 or nursery. These 2 follow-up consultations will ensure that all parents of both groups have received  
8 homogeneous key information on ASD and its management.  
9  
10

### 11 12 13 **Avoidance of contamination**

14  
15  
16 PACT is not disseminated and implement in the community, in particular in underserved area.  
17 However, PACT that might be received in the community will be reported (parent-report) [29].

18  
19 Research assessors will be separate to the therapists and will be located and supervised separately in  
20 each center.  
21

22  
23 Professionals doing the 2-follow-up consultation on ASD and its management will not be trained to the  
24 PACT therapy nor be implicated in the research assessment.  
25  
26  
27

### 28 **Measures**

#### 29 **Primary outcome**

#### 30 **To assess autism severity**

31  
32  
33 Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction  
34 based, standardized observational assessment, in communication, play, imaginative skills, and  
35 repetitive behaviors [30,31]. It is a widely used scale in the field of ASD research with good  
36 psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic  
37 symptoms [32].  
38  
39

40  
41  
42 At inclusion and after 12 months, we will use only the module 1, for 18 months old age and older  
43 children able to use no or few words.  
44

45  
46 There is a good Interrater reliability for Module 1 items [33,34] . Internal consistency Cronbach's alpha  
47 coefficients was high in original study [32]. This scale has also shown that it can measure change in  
48 autism severity [31,35,36].  
49

50  
51 ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 code the level of language,  
52 from the severity "the child is using regular use of statements with two or more words" (code 0) to  
53 "the child has no spontaneous use of approximate words or words" (code 4). When the language is  
54 not enough developed ( $A1 \geq 3$ ), the two items measuring the particularity of the language in the  
55 algorithm (item A3 speech abnormalities, item A5 stereotyped language) will be scored 3 (worst value)  
56 (as already done in Green and collaborators in 2010 [11]). The minimum overall ADOS-2 module 1 raw  
57 score will be 0 and the maximum score 42. A higher score means more autistic symptoms.  
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3 Our primary outcome will be the change between baseline and 12 month in the overall raw score in  
4 reciprocal socio-communicative interactions and repetitive and restrictive behaviors in line with the  
5 DSM-V [30,37]  
6

7  
8 Researcher will be trained to achieve recognized standards. Regular reliability meetings of all  
9 researchers with discrepant ratings being addressed to maintain researcher calibration.  
10

11 **Secondary outcomes** (See appendix 1 for more detailed)  
12

13 **To assess social communication and interaction in the natural setting of parent-child interaction at**  
14 **home :**  
15

16 -*Brief Observation of Social Communication Change (BOSCC)*[38].  
17

18 **To assess dyadic communication in the natural setting of parent-child interaction at home:**  
19

20 -*Dyadic Communication Measure for Autism (DCMA)* [28].  
21

22 **To assess child cognitive development:**  
23

24 -*Mullen Scales of Early Learning (MSEL)* [27]  
25

26 **To assess child language development:**  
27

28 -“Development of expressive language”, (*Development du Language de Production In*  
29 *french\_DLPP*)[39].  
30  
31

32 **To assess Adaptative behavior of the child:**  
33

34 -*Vineland Adaptive Behaviors Scales second version (VABS-2)* [40]  
35

36 **To assess Parent’s Stress, health, priorities and experience of the family:**  
37

38 -*Autism Family Experience (AFEQ)* [41]  
39

40 -*ISP (Parental stress index)* [42].  
41

42 -*General Health Questionnaire (GHQ-28)* [43]  
43  
44

45 **To assess implementation of the intervention:**  
46

47 - *PACT Fidelity Rating Scale*  
48

49 -Number of training session done  
50

51 -Quality of videoconferencing during each session  
52

53 -Parents acceptability of videoconferencing training and implementation of PACT at home (self-report  
54 on Likert-scale)  
55

56 -Number of hours per day using PACT at home at 12 months  
57  
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3 -Parent's qualitative PACT adherence coded with DCMA on the 12 minutes home child-parent  
4 interaction  
5

### 6 **Participants timeline** (see also figure 1) 7

8  
9 Toddlers will be addressed by health professionals for suspected ASD and possibility to be enrolled in  
10 this study. We will receive the family, complete the ADI-R during the first meeting, and check the  
11 criteria for eligibility. We will then propose the complementary assessments ADOS, Mullen with the  
12 child and Vineland by videoconferencing with the parent, to complete the criteria for eligibility. When  
13 toddlers and families meet the criteria for participation, parents will be informed in detail about the  
14 study and possibility of an intervention with PACT or TAU only according to the randomisation. They  
15 will be asked to sign written informed consent if they agree to participate to the study after one week  
16 of reflection.  
17  
18

19  
20 The "referent parent" will be decided before the randomisation. Children will be subsequently  
21 randomised into intervention or control group. Parents will be informed of the result of the  
22 randomisation and complete the assessment.  
23

### 24 **Assignment of intervention** 25

#### 26 ***Allocation sequence generation and randomisation*** 27

28  
29 All eligible toddlers, with parental consent, will be assigned to the 2 study groups in a 1:1 ratio using  
30 the minimization method with the following stratification factors: the centre, the children's age, level  
31 of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a  
32 minimization algorithm with a .90 random element will be used and known only by the statistician  
33 (AD). The randomisation is centralized.  
34  
35

#### 36 ***Blinding*** 37

38  
39 Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation  
40 group. PACT therapists will not be involved in the diagnosis or assessment. An assessor blind to the  
41 allocation group will administer every assessment. Data manager and biostatistician will be blinded to  
42 the allocation groups.  
43

### 44 **Data collection and management** 45

#### 46 ***Data collection*** 47

48  
49 Data will be collected through standardized observations done by a researcher blind of the allocation  
50 and questionnaires and interviews completed by parents. We will be particularly vigilant about the  
51 measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.  
52

#### 53 ***Participation retention and follow-up*** 54

55  
56 Children of both groups will benefit from early diagnosis and assessment and will have the same follow-  
57 up evaluations over the 1-year study period in the diagnostic units. That would promote participant  
58 retention and complete follow-up. Any discontinuation of study participation will be collected with the  
59 reason.  
60

### **Data Management**

The study data will be collected on a secure electronic case report form (eCRF) that will be available at each centre through an internet portal. No personal identifying information will be mentioned on the eCRF. Each subject included in the study will be assigned a unique identification number.

All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing cabinet at each centre. Access to these files will be limited to research staff involved in the study.

The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.

### **Statistical analysis**

#### **Simple size calculation**

On the basis of the findings of PACT Trial (Green, 2010), we have powered the study to be able to detect a difference in change overall ADOS score of 2 points. The group difference in mean change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group). The pre and post measures were correlated at 0.67. Therefore, the most conservative values were fixed for ADOS standard deviation and for correlation among the repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide about 80% power for the study.

#### **Feasibility of recruitment**

A strong partnership with ASD orientation platforms, recently implanted in France, a broad communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will allow to reach the sample size over 2 years.

#### **Statistical analysis**

A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will be reported at 12 months endpoint in accordance with the CONSORT 2010 statement. No interim analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Baseline characteristics will be presented in each group.

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2  
3 Summary statistics will be presented for process variables (number of PACT sessions, quality of  
4 videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours  
5 declared to be realized with the child) to show the feasibility and acceptability of PACT implementation  
6 in the intervention group.  
7

8  
9 The pattern of missing data will be investigated (number and mechanism of missingness). Missing data  
10 strategies can be applied and sensitivity analysis of different strategies (simple or multiple imputation)  
11 will be conducted.  
12

13  
14 A repeated measures analysis will be used to test the effect of PACT intervention on overall ADOS  
15 module 1 score over the 12-month study period. A linear mixed model will be run with the overall  
16 ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or  
17 TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random  
18 effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-  
19 2) and gender) and baseline variables that showed evidence of treatment group imbalance. Time will  
20 be represented by dummy variable. Model assumption will be verified according to residual analysis.  
21 If most of assumptions are not met other alternative such as transformation for ADOS overall raw score  
22 can be examined. Sensitivity analyses like complete case and per-protocol analysis can be performed  
23 to assess the robustness of the results to protocol deviations. In complete case analysis, only patient  
24 with primary outcome documented will be analyzed. In per-protocol participants who violate the  
25 protocol will be excluded from the analysis.  
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30 All the secondary outcomes (Overall total score of the BOSCC, Initiative of communication and  
31 synchrony measured with the DCMA, overall raw score of the MSEL in receptive and expressive  
32 language, overall score in expressive language of the DLFP, overall raw score, Communicative and  
33 social raw score at the VABS, Parental Stress Indice, Parent General Health score, AFEQ score) will be  
34 analyzed in a similar way using when appropriate linear or generalized linear mixed models. Tobit  
35 models should be used to address potential floor effects.  
36  
37

38 We will finally explore the parent's and children's characteristics, moderating the implementation and  
39 efficacy of this therapy. We will also test the previously found mediators implicated in the efficacy of  
40 this therapy (Pickles, 2017).  
41  
42  
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44

### 45 **Qualitative analysis of barriers and facilitators of implementation**

46  
47 Based on the speech of the parents and of the therapists we will describe the facilitators and barriers  
48 of the implementation of video-conferencing PACT.  
49

50  
51 The data will be collected through semi-structured interview and will be analysed with the classical  
52 technique of Interpretative Phenomenological Analysis (IPA) [44] Population selection will follow the  
53 rules of the purposive sampling and will allow a maximal variation of the sample [45]. An estimation  
54 of 30-60 parents will be necessary to reach data saturation based on previous studies [46-48]. The  
55 total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we  
56 will explore different area in links with barriers and obstacles about learning and implementing PACT  
57 by videoconferencing. A guide for the interview will be elaborated in the initial phase of the project  
58  
59  
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1  
2  
3 based on first interviews. Interview will be recorded, and the verbatim will be transcribed to analysis  
4 the entirely communication of the participant.  
5

6  
7 Data from the quantitative and qualitative sources in the process evaluation will analysed separately.  
8 Then, the results of the qualitative study will be integrated with the quantitative results to optimize  
9 the findings [49].  
10

## 11 **Monitoring**

12  
13 Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent  
14 representatives and associate researcher composed the trial steering committee (TSC). The TSC is  
15 independent of sponsor and funders and have no competing interests. The TSC has developed the  
16 study protocol and is responsible for data collection, management, publications and the final data  
17 set.  
18  
19

20  
21 The coordinating center is independent from the centers for investigation.  
22

23 According to the French law, the study required a formal data monitoring who will be done by the  
24 sponsor. Annual report to the funders will be also ensured.  
25

### 26 ***Adverse effect***

27  
28 No specific suffer harm from trial participation is anticipated.  
29

30  
31 However, as required by the French law, adverse events will be collected all along the study and  
32 reported in the eCRF section. Description of the event, date of occurrence, intensity, severity,  
33 accountability will be reported. Outcomes of this event and action taken after its report will also be  
34 concealed.  
35

36  
37 We anticipate that the early assessment, follow-up consultation on ASD and its management will help  
38 and support the both groups during the post-diagnosis period. Hence, no post-trial care is planned.  
39

### 40 ***Trial status***

41  
42 The trial status is currently Recruiting. The study has started the 30th June 30, 2020.  
43

44  
45 **Ethics and Dissemination:** This study is approved by the French Institutional Review Board (reference  
46 No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also  
47 disseminate via national and international, general and specialist, meeting and through the parent  
48 association (<https://Bleunetwork.fr>; <https://autisme-ambitionavenir.com>; [desailespourgrandir.org](https://desailespourgrandir.org)).  
49 An individual feedback to the participant will be done through a regular newsletter. We will adhere  
50 to defined authorship criteria as per the International Committee of Medical Journal Editors.  
51

52  
53 **Author contribution:** MMG and ST, PO, LJ conceived and design the project, and MMG is leading the  
54 coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding. LJ  
55 and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ  
56 contributed to the sample size calculation, the randomisation procedure and the statistical plan, and  
57 are responsible for data management, randomisation and statistical analysis. JG contributed to the  
58 protocol. ARL contributed to the protocol of the qualitative study. CA and NG to the PACT training  
59 and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible for recruitment  
60



1  
2  
3 and evaluation of children. SG contributed to draft the paper. All authors critically reviewed and  
4 approved the final version of the manuscript.  
5

6 **IFPAD Study group:** Mrs Pauline Auphan (psychologist), Mrs Laetitia Bouveret (research assistant),  
7 Mrs Laurie Herman (research assistant), Dr Anne-Laure Toureille (PACT trainer), Mrs Lucie Jansen  
8 (PACT trainer), Dr Sandrine Sonié (CRA Lyon), Pr. Mario Speranza (CHU Versailles), Pr. Bruno Falissard  
9 (Paris), Pr Nicolas Georgieff (Lyon), Dr Matias Winter (HCL), Mrs Nadège Alloisio (parent association),  
10 Mr Chams-Ddine BELKHAYAT (parent association).  
11  
12

13 **Patient and Public Involvement subsection:** Mrs Alloisio (Association AAA <https://autisme-ambitionavenir.com>) and Mr Belkhatat (association <https://bleunetwork.fr/pro>) are parent of a child  
14 with autism and represents two different association. They are part of the steering committee.  
15  
16  
17

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19 Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by  
20 the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched  
21 for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national  
22 de la santé et de la recherche médicale (Inserm) ( IReSP-17-Autisme3-16).  
23  
24  
25

26 **Disclaimer:** The funders and sponsor have no role in study design, data collection, management, data  
27 analysis and interpretation of data, in the writing of the report or in the decision to submit the  
28 manuscript for publication.  
29  
30

31 **Competing interests' statement:** None declared.  
32

33 **Consent:** Obtained from the both parents of the child.  
34  
35

36 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
37

38 **Data sharing statement:** The trial statisticians will have access to the data set for the analysis of trial  
39 outcomes. The PI will have access to the data and will take full responsibility for the analysis and  
40 publication of the results. Once the main analyses have been undertaken, data will be available to  
41 principal and other investigators subject to approval of data analysis plans by the steering  
42 committee.  
43  
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## 45 References

- 46  
47 1 Baghdadli A, Miot S, Rattaz C, *et al.* Investigating the natural history and prognostic factors  
48 of ASD in children: the multicentric Longitudinal study of childrEN with ASD-the ELENA study  
49 protocol. *BMJ Open* 2019;**9**:e026286.  
50
- 51 2 Elsabbagh M, Divan G, Koh Y-J, *et al.* Global Prevalence of Autism and Other Pervasive  
52 Developmental Disorders. *Autism Research* 2012;**5**:160–79. doi:10.1002/aur.239  
53
- 54 3 Fombonne E. The Prevalence of Autism. *JAMA* 2003;**289**:87–9. doi:10.1001/jama.289.1.87  
55
- 56 4 Howlin P. Living with impairment: The effects on children of having an autistic sibling.  
57 *Child: care, health and development* 1988;**14**:395–408.  
58
- 59 5 HAS. Trouble du spectre de l'autisme Signes d'alerte, repérage, diagnostic et évaluation chez  
60

1  
2  
3 l'enfant et l'adolescent. 2018;:45.

4  
5 6 Geoffroy M-M, Thevenet M, Georgieff N. News in early intervention in autism. *Psychiatr*  
6 *Danub* 2016;**28**:66–70.

7  
8 7 Touzet S, Occelli P, Schröder C, *et al.* Impact of the Early Start Denver Model on the  
9 cognitive level of children with autism spectrum disorder: study protocol for a randomised controlled  
10 trial using a two-stage Zelen design. *BMJ open* 2017;**7**:e014730.

11  
12 8 Zwaigenbaum L, Bauman ML, Choueiri R, *et al.* Early intervention for children with autism  
13 spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics*  
14 2015;**136**:S60–S81.

15  
16 9 French L, Kennedy EMM. Annual Research Review: Early intervention for infants and young  
17 children with, or at-risk of, autism spectrum disorder: a systematic review. *J Child Psychol Psychiatry*  
18 2018;**59**:444–56. doi:10.1111/jcpp.12828

19  
20 10 Oono IP, Honey EJ, McConachie H. Parent-mediated early intervention for young children  
21 with autism spectrum disorders (ASD). *Evidence-Based Child Health: A Cochrane Review Journal*  
22 2013;**8**:2380–2479.

23  
24 11 Green J, Charman T, McConachie H, *et al.* Parent-mediated communication-focused treatment  
25 in children with autism (PACT): a randomised controlled trial. *The Lancet* 2010;**375**:2152–2160.

26  
27 12 Pickles A, Le Couteur A, Leadbitter K, *et al.* Parent-mediated social communication therapy  
28 for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet*  
29 2016;**388**:2501–9. doi:10.1016/S0140-6736(16)31229-6

30  
31 13 Green J, Garg S. Annual Research Review: The state of autism intervention science: progress,  
32 target psychological and biological mechanisms and future prospects. *Journal of Child Psychology*  
33 *and Psychiatry* 2018;:424–43. doi:10.1111/jcpp.12892@10.1111/(ISSN)1469-  
34 7610.Jack\_Tizard\_VI\_Autism\_Learning\_Disabilities

35  
36 14 Lord, C., Rutter, M., DiLavore, P.C, *et al.* *ADOS. Autism Diagnostic Observation Schedule,*  
37 *second edition (ADOS-2). Manual (part I): Modules 1–4.* Torrane. CA Western Psychological  
38 Services. 2012b.

39  
40 15 Pickles A, Harris V, Green J, *et al.* Treatment mechanism in the MRC preschool autism  
41 communication trial: implications for study design and parent-focussed therapy for children. *J Child*  
42 *Psychol Psychiatry* 2015;**56**:162–70. doi:10.1111/jcpp.12291

43  
44 16 Vismara LA, McCormick CEB, Wagner AL, *et al.* Telehealth Parent Training in the Early  
45 Start Denver Model: Results From a Randomized Controlled Study. *Focus Autism Other Dev Disabl*  
46 2018;**33**:67–79. doi:10.1177/1088357616651064

47  
48 17 Vismara LA, McCormick C, Young GS, *et al.* Preliminary Findings of a Telehealth Approach  
49 to Parent Training in Autism. *J Autism Dev Disord* 2013;**43**:2953–69. doi:10.1007/s10803-013-1841-8

50  
51 18 Green J, Aldred C, Charman T, *et al.* Paediatric Autism Communication Therapy-Generalised  
52 (PACT-G) against treatment as usual for reducing symptom severity in young children with autism  
53 spectrum disorder: study protocol for a randomised controlled trial. *Trials* 2018;**19**:514.  
54 doi:10.1186/s13063-018-2881-3

- 1  
2  
3 19 Khan K, Hall CL, Davies EB, *et al.* The Effectiveness of Web-Based Interventions Delivered  
4 to Children and Young People With Neurodevelopmental Disorders: Systematic Review and Meta-  
5 Analysis. *J Med Internet Res* 2019;**21**:e13478. doi:10.2196/13478  
6
- 7 20 Bearss K, Burrell TL, Challa SA, *et al.* Feasibility of Parent Training via Telehealth for  
8 Children with Autism Spectrum Disorder and Disruptive Behavior: A Demonstration Pilot. *J Autism*  
9 *Dev Disord* 2018;**48**:1020–30. doi:10.1007/s10803-017-3363-2  
10  
11
- 12 21 Richards DA, Bazeley P, Borglin G, *et al.* Integrating quantitative and qualitative data and  
13 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
14 doi:10.1136/bmjopen-2019-032081  
15
- 16 22 Fetters MD, Curry LA, Creswell JW. Achieving Integration in Mixed Methods Designs-  
17 Principles and Practices. *Health Serv Res* 2013;**48**:2134–56. doi:10.1111/1475-6773.12117  
18  
19
- 20 23 Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: A revised version of  
21 a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J*  
22 *Autism Dev Disord* 1994;**24**:659–85. doi:10.1007/BF02172145  
23
- 24 24 Lord C, Risi S, Lambrecht L, *et al.* Autism Diagnostic Observation Schedule-Generic : A  
25 standard measure of social and communication deficits associated with the spectrum of autism.  
26 *Journal of Autism and Developmental Disorders* 2000;**30**:223.  
27
- 28 25 Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism  
29 spectrum disorders. *Journal of autism and developmental disorders* 2009;**39**:693–705.  
30  
31
- 32 26 Kim SH, Thurm A, Shumway S, *et al.* Multisite Study of New Autism Diagnostic Interview-  
33 Revised (ADI-R) Algorithms for Toddlers and Young Preschoolers. *J Autism Dev Disord*  
34 2013;**43**:1527–38. doi:10.1007/s10803-012-1696-4  
35
- 36 27 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.  
37  
38
- 39 28 Aldred C, Green J, Emsley R, *et al.* Brief report: Mediation of treatment effect in a  
40 communication intervention for pre-school children with autism. *Journal of autism and developmental*  
41 *disorders* 2012;**42**:447–454.  
42
- 43 29 Dunn G, Emsley R, Liu H, *et al.* Evaluation and validation of social and psychological  
44 markers in randomised trials of complex interventions in mental health: a methodological research  
45 programme. *Health Technology Assessment* 2015;**19**. doi:10.3310/hta19930  
46  
47
- 48 30 Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism  
49 spectrum disorders. *Journal of autism and developmental disorders* 2009;**39**:693–705.  
50
- 51 31 Lord C, Risi S, Lambrecht L, *et al.* The Autism Diagnostic Observation Schedule—Generic:  
52 A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism.  
53 *J Autism Dev Disord* 2000;**30**:205–23. doi:10.1023/A:1005592401947  
54
- 55 32 McConachie H, Parr JR, Glod M, *et al.* Systematic review of tools to measure outcomes for  
56 young children with autism spectrum disorder. *Health Technology Assessment* 2015;**19**:1–506.  
57 doi:10.3310/hta19410  
58
- 59 33 Kamp-Becker I, Ghahreman M, Smidt J, *et al.* Dimensional Structure of the Autism  
60

1  
2  
3 Phenotype: Relations Between Early Development and Current Presentation. *J Autism Dev Disord*  
4 2009;**39**:557–71. doi:10.1007/s10803-008-0656-5

5  
6 34 Lord C, Risi S, Lambrecht L, *et al.* Autism Diagnostic Observation Schedule-Generic : A  
7 standard measure of social and communication deficits associated with the spectrum of autism.  
8 *Journal of Autism and Developmental Disorders* 2000;**30**:223.

9  
10 35 Green J, Charman T, McConachie H, *et al.* Parent-mediated communication-focused treatment  
11 in children with autism (PACT): a randomised controlled trial. *The Lancet* 2010;**375**:2152–2160.

12  
13 36 Pickles A, Le Couteur A, Leadbitter K, *et al.* Parent-mediated social communication therapy  
14 for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet*  
15 2016;**388**:2501–9. doi:10.1016/S0140-6736(16)31229-6

16  
17 37 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th*  
18 *ed.)*. Washington, DC. 2013.

19  
20 38 Grzadzinski R, Carr T, Colombi C, *et al.* Measuring Changes in Social Communication  
21 Behaviors: Preliminary Development of the Brief Observation of Social Communication Change  
22 (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9

23  
24 39 Bassano D, Labrell F, Bonnet P. Le Développement du langage de production en français  
25 (DLPF) entre 18 et 42 mois : une synthèse. *Enfance* 2020;**N°2**:151. doi:10.3917/enf2.202.0151

26  
27 40 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS  
28 Pearson 2005.

29  
30 41 Leadbitter K, Aldred C, McConachie H, *et al.* The Autism Family Experience Questionnaire  
31 (AFEQ): An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life  
32 and Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62.  
33 doi:10.1007/s10803-017-3350-7

34  
35 42 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire :  
36 validation et normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier et  
37 Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar

38  
39 43 Pariente P, Challita H, Mesbah M, *et al.* The GHQ-28 questionnaire in French : a validation  
40 survey in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.

41  
42 44 Smith JA, Shinebourne P. Interpretative phenomenological analysis. In: Cooper H, Camic PM,  
43 Long DL, *et al.*, eds. *APA handbook of research methods in psychology, Vol 2: Research designs:  
44 Quantitative, qualitative, neuropsychological, and biological*. Washington: : American Psychological  
45 Association 2012. 73–82. doi:10.1037/13620-005

46  
47 45 Guba EG, Lincoln. *Fourth generation evaluation*. Sage Publications, Inc. 1989.

48  
49 46 Lachal J, Speranza M, Taïeb O, *et al.* Qualitative research using photo-elicitation to explore  
50 the role of food in family relationships among obese adolescents. *Appetite* 2012;**58**:1099–105.  
51 doi:10.1016/j.appet.2012.02.045

52  
53 47 Gorse P, Nordon C, Rouillon F, *et al.* Subjective Motives for Requesting In-Patient Treatment  
54 in Female with Anorexia Nervosa: A Qualitative Study. *PLoS ONE* 2013;**8**:e77757.

1  
2  
3 doi:10.1371/journal.pone.0077757  
4

5 48 Morse JM. The Significance of Saturation. *Qual Health Res* 1995;**5**:147–9.  
6 doi:10.1177/104973239500500201  
7

8 49 Richards DA, Bazeley P, Borglin G, *et al*. Integrating quantitative and qualitative data and  
9 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
10 doi:10.1136/bmjopen-2019-032081  
11  
12  
13  
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15  
16  
17  
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For peer review only

Figure 1. Flow-chart of the study.

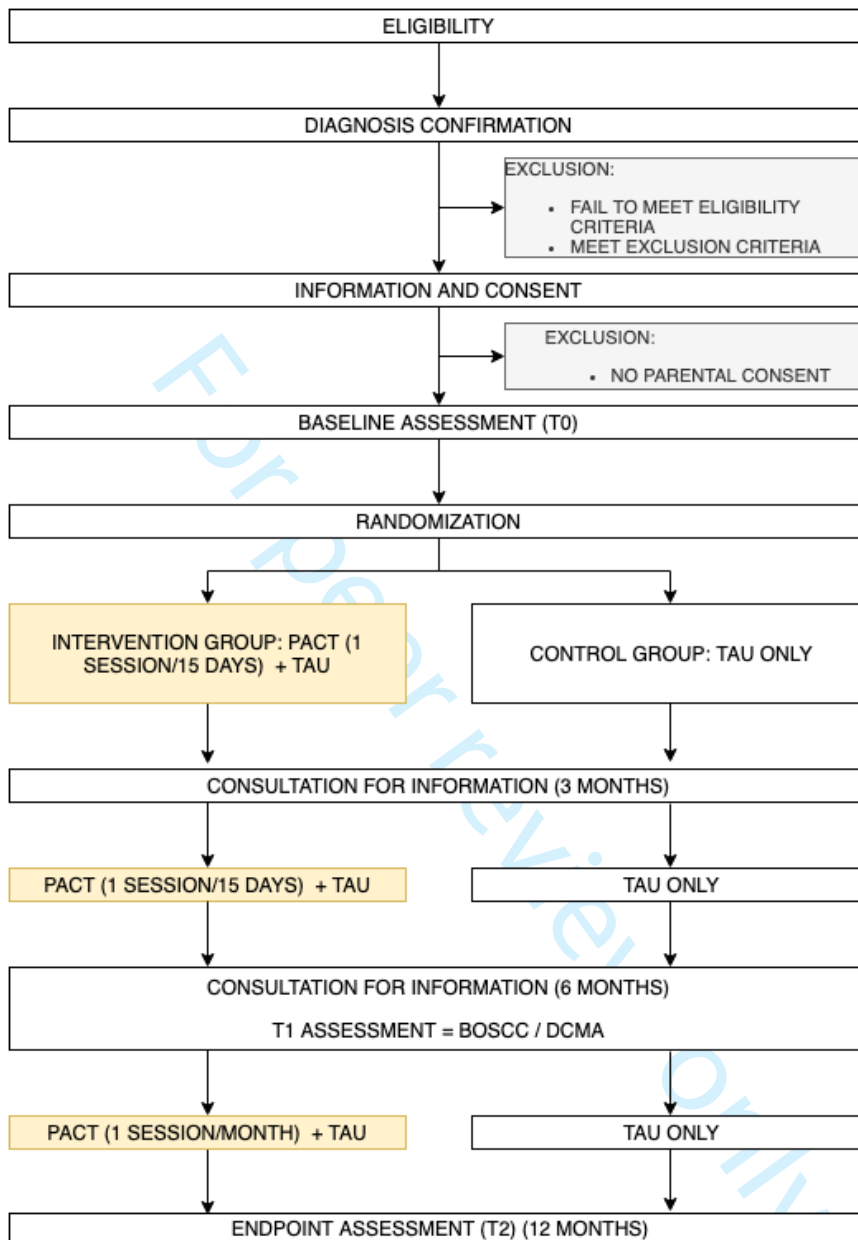


Figure 1. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	Enrolment	T0 baseline	T1 6 months	T2 12 months
<b>Eligibility screen</b>				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
<b>Intervention</b>				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home			—————→	
Treatment as usual			—————→	
<b>Assessment</b>				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
Implementation:				
Number of PACT training session with the professional				x
Mean of quality of videoconferencing collected after each session				x
Number of hours declared by parents using PACT at home				x



Qualitative interview (around 35 parents in the PACT intervention group) and all the therapists					x
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Figure 3- WHO trial registration data set

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) ( IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
Contact for public queries	Marie-Maude Geoffray (PI), email: marie-maude.geoffray @ch-le-vinatier.fr Lucie Jurek, email : lucie.jurek@ch-le-vinatier.fr Pauline Occelli, email: pauline.occelli@chu-lyon.fr
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Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recruitment	France



Data category	Information
Health condition or problem studied	Autism spectrum disorder (ASD)
Interventions	<p><i>Intervention:</i> PACT for toddlers and young children with ASD  <i>Description:</i> PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months.  <i>Control:</i> care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.</p>
Key inclusion and exclusion criteria	<p><i>Age:</i> between 18 and 36 months  <i>Sex:</i> male or female  <i>Inclusion criteria:</i> diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center.  <i>Exclusion criteria:</i> serious neurological or physical condition, family unavailable for a regular follow-up.</p>
Study type	<p>Interventional  <i>Allocation:</i> randomized 1:1; parallel assignment; blinding: assessor blind</p>
Date of first enrolment	15th July 2020
Target sample size	238
Recruitment Status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.

## Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

### To assess social communication and interaction in the natural setting of parent-child interaction at home

*Brief Observation of Social Communication Change (BOSCC)* measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

### To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).

1  
2  
3 Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated  
4 and retro-translated for the purpose of a previous study [2]  
5

6 It can be used to code a number of acts of communication per timepoint. A higher score indicates  
7 better communication.  
8

9 Coding will be done on the same 12 minutes home parent-child video described above in BOSCC.  
10

### 11 **To assess child cognitive development**

12  
13  
14 The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68  
15 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure  
16 in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively  
17 as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X  
18 syndrome, and speech delays [5–7]  
19

20  
21 Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for  
22 the purpose of a previous study [2]  
23

24  
25 Scoring varies by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point  
26 scale. Results for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age  
27 equivalents. An overall score is also measured (M=100, SD=15). A higher score means better skills.  
28

### 29 **To assess child language development**

30  
31 The “development of expressive language”, a standardised French Scale (Development du Language  
32 de Production In french\_DLPF), is based on a self-administered parent-report [8]. This measure is  
33 standardised for age. Only the level 4 of the DLFP will be administered at each assessment to have a  
34 continuous score on expressive language.  
35

36  
37 The DLFP was validated in a study [3].  
38

39  
40 Score is calculated based on the number of words in the naturalistic environment of the child as  
41 reported by the parents. A higher score means better language skills.  
42

43 It will complete the measure of functional communication with VABS-2 and standardised measure with  
44 MSEL.  
45

### 46 **Adaptative behavior**

47  
48 Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the  
49 child’s daily personal and social skills [9]. This measure will be collected via a parental interview over  
50 videoconferencing before the inclusion and at 12 months. This measure will provide an estimate of  
51 any assesses functional change in socialization, communication, motor and daily living skills, based on  
52 parent observation in the naturalistic settings of the child.  
53

54  
55 The VABS has well-established psychometric properties [9,10]. It is validated in french.  
56  
57  
58  
59  
60

1  
2  
3 All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to  
4 '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score  
5 is described by normalized score (M=100, SD=15). A higher score means better adaptative skills.  
6  
7

### 8 **To assess Parent's Stress, health, priorities and experience of the family**

9  
10 The psychometry of the following tools are described in the manual of each tool.  
11

12  
13 *Autism Family Experience (AFEQ)* [11] is a self-administered parent report about quality of life and  
14 priorities for early intervention. It is composed of 4 subscales (experience of being a parent, family life,  
15 child development understanding and relationships, child symptoms) and has an overall score. It was  
16 translated and retro-translated for the purpose of this study with the author. A higher score means  
17 better experience.  
18

19  
20 *ISP (Parental stress index)* is a 36-item self-administered parent report to measure the stress in the  
21 parent-child system. We will use the short form of the 4th edition. A validated French version exists  
22 [12]. A higher score means more stress.  
23

24  
25 *General Health Questionnaire (GHQ-28)* is a self-administered parent report, 28 item scaled version,  
26 assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. There  
27 is an overall score of 60. [13] A higher score means more health problems.  
28

### 29 **To assess implementation of the intervention**

30  
31  
32 *Professional adherence to the treatment:*

33  
34 All therapy training sessions with professionals will be videotaped and will be independently rated by  
35 the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across  
36 the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual  
37 including the style of training.  
38

39  
40 *Acceptability and feasibility of the PACT session*

41  
42 The therapist will collect the number of the session done with each parent and also the quality of  
43 videoconferencing during the session with the professional. Quality of sound and quality of the image  
44 will be rated with a 4-points Linkert scale. The number of disconnections along the session will also be  
45 collected.  
46

47  
48 The parents will self-report (likert-scale) the acceptability of videoconferencing training and  
49 implementation of PACT at home.  
50

51  
52 *Parent PACT adherence at home*

53  
54 At 12 months, Parents will declare the average number of hours per day using PACT at home outside  
55 the PACT session with the therapist.  
56

57  
58 DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative  
59 adherence of PACT intervention.  
60

- 1 Grzadzinski R, Carr T, Colombi C, *et al.* Measuring Changes in Social Communication Behaviors: Preliminary Development of the Brief Observation of Social Communication Change (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9
- 2 Touzet S, Ocelli P, Schröder C, *et al.* Impact of the Early Start Denver Model on the cognitive level of children with autism spectrum disorder: study protocol for a randomised controlled trial using a two-stage Zelen design. *BMJ open* 2017;**7**:e014730.
- 3 Aldred C, Green J, Emsley R, *et al.* Brief report: Mediation of treatment effect in a communication intervention for pre-school children with autism. *Journal of autism and developmental disorders* 2012;**42**:447–454.
- 4 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.
- 5 Burns TG, King TZ, Spencer KS. Mullen Scales of Early Learning: The Utility in Assessing Children Diagnosed With Autism Spectrum Disorders, Cerebral Palsy, and Epilepsy. *Applied Neuropsychology: Child* 2013;**2**:33–42. doi:10.1080/21622965.2012.682852
- 6 Bishop SL, Guthrie W, Coffing M, *et al.* Convergent validity of the Mullen Scales of Early Learning and the differential ability scales in children with autism spectrum disorders. *American journal on intellectual and developmental disabilities* 2011;**116**:331–343.
- 7 Farmer C, Golden C, Thurm A. Concurrent validity of the differential ability scales, second edition with the Mullen Scales of Early Learning in young children with and without neurodevelopmental disorders. *Child Neuropsychology* 2016;**22**:556–69. doi:10.1080/09297049.2015.1020775
- 8 Bassano D, Labrell F, Champaud C, *et al.* Le DLPF : un nouvel outil pour l'évaluation du développement du langage de production en français. *Enfance* 2005;**57**:171. doi:10.3917/enf.572.0171
- 9 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS Pearson 2005.
- 10 Chatham CH, Taylor KI, Charman T, *et al.* Adaptive behavior in autism: Minimal clinically important differences on the Vineland-II: Adaptive behavior and autism. *Autism Research* 2018;**11**:270–83. doi:10.1002/aur.1874
- 11 Leadbitter K, Aldred C, McConachie H, *et al.* The Autism Family Experience Questionnaire (AFEQ): An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life and Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62. doi:10.1007/s10803-017-3350-7
- 12 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire : validation et normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier et Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar
- 13 Pariente P, Challita H, Mesbah M, *et al.* The GHQ-28 questionnaire in French : a validation survey in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.

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## Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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# Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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## Abstract

Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is a parent-mediated therapy that has shown significant and sustained impact on autism symptom reduction. However, the access to such evidence-based therapies for families is limited due to autism centers located in large urban areas. Using videoconferencing to deliver PACT training to parents may improve accessibility for families living in underserved areas.

This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a telehealth, videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12-month period. It will compare PACT plus treatment as usual (TAU) against TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 minutes away from the specialist centres for autism. Primary outcome will be the change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analysis will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

## Article Summary

### Strengths and limitations of this study

- Large multicentre RCT in children with ASD under 3 years old, testing remote delivery of an evidenced intervention
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved area
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists will not be blind to the allocation group.

**Keys Words:** Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

**Trial registration:** ClinicalTrials.gov Identifier: NCT04244721

## Introduction

### Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of at least 1.5% in developed countries and can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months of age [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years have the potential for maximal impact on autism symptom severity.

Therapies can be delivered by therapists, teachers and parents [6]. For preschool children with ASD, parent-mediated therapies can empower parents to face challenging social interaction with their children[7,8]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication Therapy) has shown significant short and long-term efficacy on objectively assessed autism symptoms in children aged from 2 to 10 years in a large UK cohort (N=152); as showed in recent systematic review [9] and meta-analysis [10]. In PACT, parents are guided by a therapist via video feedback to optimize their interactive behaviours in order to enhance parent-child dyadic interaction, which in turn impacts on child language, communication and autism symptoms (PACT reference) [11]. In a trial of PACT intervention compared to regular care, PACT showed a statistically significant effect at 13 month endpoint to reduce of autism symptom severity measured on Autism diagnostic Observation Schedule version 2 (ADOS-2) (effect size 0.64; 95%CI 0.07-1.20); and an increase in parental communication synchrony with the child and child communication initiations with the parent [12]. The follow-up study showed evidence of sustained effect on autism symptom severity six years after intervention end, with a significant overall reduction in symptom severity over the course of trial and follow-up period (effect size=0.55, 95% CI 0.14 to 0.91, p=0.004)[13]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiations, which in turn was mediated by improved parent-child synchrony [14].

Availability of PACT therapy is limited; even more so in rural settings or in regions away from specialist centres. Training parents to PACT via videoconferencing conducted by trained therapists may be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to successfully provide parent-mediated therapy in autism by videoconference [15,16]. The team who developed the PACT therapy had a positive experience of parent guidance by videoconferencing (C. Aldred and J. Green, personal communication, June 10, 2020). Indeed, remote PACT was partly used, during some session, in a recent RCT [17]. However, PACT has never been evaluated when exclusively delivered by videoconference. The barriers and facilitators of videoconferencing therapy are not sufficiently well known, and hence it is also essential to address them properly [18,19].

Research question: The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness on autistic symptom severity and other measures of PACT therapy delivered to parents by videoconference.

A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

1  
2  
3 The hypothesis is that PACT intervention delivered by videoconferencing + TAU (Treatment As Usual)  
4 will have a superior efficacy on child autism symptom severity as compared to TAU alone.  
5  
6  
7  
8

## 9 **Objectives**

10  
11 Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, in which  
12 professionals guide parents via videoconferencing over a 12-months period, on overall autistic  
13 symptoms measured with a standardized measure, the Autism Diagnostic Observation Schedule 2  
14 (ADOS), in children with ASD aged from 18 to 36 months at inclusion, living in underserved area.  
15  
16

17 Our secondary objectives will be to evaluate the development of child socio-communicative  
18 interactions, language, communication initiation and daily adaptive behaviour. At the parent level, we  
19 will evaluate the intervention effects on stress, health and family priorities.  
20  
21

22 The implementation of the therapy will be evaluated through the adherence of professionals and  
23 parents to PACT, and through parents and professionals' acceptability and feasibility of the PACT  
24 sessions.  
25  
26  
27  
28

## 29 **Method**

### 30 **Study design**

31  
32 Our study is a multicentre, prospective, 2 parallel group, 1:1 ratio, single blind randomised controlled  
33 trial (RCT) comparing PACT intervention + Treatment As Usual (TAU) against TAU alone. Evaluation is  
34 based on a mixed-method approach combining quantitative and qualitative studies [20,21].  
35  
36  
37  
38

39 A qualitative study will be conducted to capture further experience of the implementation of the  
40 intervention and causal pathway of effectiveness or ineffectiveness according to the therapists' and  
41 the parents' experience.  
42  
43

44 Figure 1 shows consort flow-chart of the study.  
45  
46

### 47 **Setting**

48  
49 We will run this trial in six academic centres in France. These centres are located in child and adolescent  
50 public hospitals. All centres have a unit for ASD diagnosis and assessment and a distinct unit for  
51 intervention where therapists have been trained in PACT and can provide PACT via videoconferencing.  
52 The Children receiving intervention come from a French-speaking population including  
53 socioeconomically disadvantaged groups.  
54  
55

### 56 **Population**

#### 57 ***Inclusion criteria***

Children will be included if they meet the following criteria:

- i) aged between 18-36 months old at referral
- ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised). For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will have to be greater or equal to 4. The score on the ADI-R algorithm for toddlers will have to be greater or equal to 11 [22]. The diagnosis will be confirmed by a multidisciplinary team specialised in Autism Spectrum Disorder diagnosis and assessment based in the academic departments of the hospitals.
- iii) have a non-verbal age equal to or above 12 months on the Mullen Scale of Early learning ( MSEL) [23].
- iiii) live more than 40 minutes away from a Center for Resources in Autism (regional center)

Referred parents will be included if they meet the following criteria:

- ii) speak French with their children
- iii) are able to use videoconferencing methods with therapists who will be based at the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing) (see Appendix 1 for details)

#### ***Exclusion criteria***

Exclusion criteria will be as follows for the child:

- i) a twin brother or sister with ASD or a brother or sister having already been included in the study
- ii) diagnosed with epilepsy requiring medication
- iii) have a severe hearing or visual impairment
- iv) an identification of a genetic anomaly which may impact on their ability to participate in the intervention or on data validity (determined by the principal investigator on a case-by-case basis).

Exclusion criteria will be as follows for the referred parents (at least one parent with):

- i) severe hearing or visual impairment
- ii) severe psychiatric disorder
- iii) unstable somatic disorders preventing participation in the intervention
- iv) lack of internet provision
- v) not available for regular intervention and follow-up
- vi) opposition of one parent to the child's participation in the study
- vii) currently undertaking PACT therapy

#### **Intervention conducted in the experimental group**

##### ***Eligibility criteria for PACT therapist and adherence***

The therapists included will be speech language pathologists, occupational therapists, clinical nurse, psychologists or child and adolescent psychiatrists, all specialised in autism. The therapists have already received formal training and supervision in PACT with the team who developed this training [12,24]. The lead therapist will organize regular meetings between therapists of all centers, with

1  
2  
3 scoring and feedback of videotaped therapy session of the study, in order to maintain a high fidelity to  
4 the therapy.  
5

### 6 ***PACT treatment principles***

7  
8 As previously described [17], parents will be trained, via video-feedback, to identify and set key  
9 strategies facilitating the socio-communicative interactions between their child and themselves.  
10 Parents will also be encouraged to use PACT every day outside the training session at least half an hour  
11 per day. The therapy follows a six-staged approach based on child developmental progression and  
12 strategies for establishing fundamental skills for the socio-communicative development. The first two  
13 stages aim to increase parent's identification of child focus and interest, synchrony, responsiveness  
14 and sensitivity to the child interest and communication. The third and fourth stages are targeted  
15 towards developing expression and comprehension of the child by commenting and modelling  
16 language adapted to the child's developmental level. Child communication initiation is also improved  
17 in the fifth stage through different strategies such as anticipation and routine. The last stage aims to  
18 develop conversation and expansion of language for verbal children. Progression from one stage to  
19 the next depends on predefined criteria.  
20  
21  
22  
23

24  
25 Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with  
26 the therapist over the 12 months [12,13]: 1-hour sessions every fortnight during 6 months to learn  
27 PACT strategies then 1 hour sessions per month over the last 6 months to maintain the capacity of  
28 parents to deliver the strategies.  
29

30  
31 Therapist will train only one parent per family and maintain fidelity to the therapy manual. The  
32 "referent parent" will have to be designated before the randomisation of the child. If the referent  
33 becomes unavailable, the therapy will stop or will continue with the other parent if possible and this  
34 change will be reported.  
35

### 36 ***Parent training session with the professional via videoconferencing***

37  
38  
39 Before each session, the parent will be asked to send a 10-minute video of their interaction with his/  
40 her child to the therapist via a secure cloud link. During the videoconferencing session (as in face-to-  
41 face intervention), referent parent will begin with a 5-minute discussion about progress since the last  
42 session. The therapist will then share his/her screen and watch together with the parent the home-  
43 based 10-minute video. They will identify, review and discuss specific clips that demonstrate  
44 accomplishment of therapy goals for the relevant stage of the PACT programme. The therapist's role  
45 will be to guide parents to identify their successful strategies and responses (i.e. episodes of  
46 engagement and/ or mutual sharing with their child). Parents will be helped to reflect on their role in  
47 enhancing interaction and to identify new intervention goals.  
48  
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50

### 51 ***Parent PACT implementation in daily life outside the therapy session***

52  
53  
54 At the end of each session, the therapist will support the parent in setting 2-3 new goals, based on the  
55 strategies identified during the session. The therapist will encourage the parent undertake daily  
56 practice the strategies for the next session and will discuss opportunities to achieve these goals in daily  
57 routine at home for at least 30 minutes per day. Parents will be guided to embed PACT strategies in  
58  
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60

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3 diverse everyday routines in different contexts. As therapy progresses, parents will be asked to send  
4 10-minutes home videos of short daily routines in different contexts.  
5  
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7

## 8 **Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management**

9  
10  
11 Regardless of group allocation, parents will receive treatment as usual (TAU) consisting of information  
12 about ASD, management and educational support for nursery and preschool placement. Parents will  
13 be referred to any relevant care available in the community (e.g.: Speech language pathologist (SLP),  
14 occupational therapist, educator, behavioural psychologist, psychiatrist). TAU received during the  
15 course of the study will be described in both groups.  
16  
17

18  
19 Regardless of group allocation, a psychiatrist or a psychologist from each autism center will provide  
20 two supplementary 45 minutes follow-up consultations conducted by videoconferencing at 3 and 6  
21 months after inclusion. They will follow an interview guide. Three thematic areas will be systematically  
22 discussed with the parents: ASD information, access to treatment in the community, support for school  
23 or nursery. These two follow-up consultations will ensure that all parents of both groups have received  
24 homogeneous key information on ASD and its management.  
25  
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28

## 29 **Avoidance of contamination**

30  
31 PACT is not currently widely implemented in the community in France, in particular in the underserved  
32 areas. Any families who are currently in receipt of PACT intervention will be excluded from this trial.  
33 However, any PACT that might be received in the community will be recorded through parent report  
34 as part of TAU [25].  
35  
36

37 Research assessors will be separate to the therapists and will be located and supervised separately in  
38 each center.  
39

40 Professionals doing the two follow-up consultation on ASD and its management will not be trained to  
41 PACT therapy nor be implicated PACT in the research assessment.  
42  
43  
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45

## 46 **Measures**

### 47 ***Primary outcome***

#### 48 **To assess autism severity**

49  
50  
51  
52 Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction  
53 based, standardized observational assessment, in communication, play, imaginative skills, and  
54 repetitive behaviours[26,27]. It is a widely used scale in the field of ASD research with good  
55 psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic  
56 symptoms [28].  
57  
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2  
3 At baseline and follow-up assessment after 12 months, we will use only ADOS-2 module 1, for children  
4 who are 18 months of age and older children who use no or few words.  
5

6 There is a good Interrater reliability for Module 1 [27]. Internal consistency Cronbach's alpha  
7 coefficients was high in original study [27]. This scale has also shown that it can measure change in  
8 autism severity [13,28].  
9

10 ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 codes the level of language,  
11 from the severity for 'the child is using regular use of statements with two or more words' (code 0) to  
12 'the child has no spontaneous use of approximate words or words' (code 4). For children with no or  
13 limited language ( $A1 \geq 3$ ), the two items measuring language in the algorithm (item A3 speech  
14 abnormalities, item A5 stereotyped language) will be scored 3 (worst value) (see Green et al. 2010  
15 [12]). The minimum overall ADOS-2 module 1 raw score will be 0 and the maximum score 42. A higher  
16 score means more autistic symptoms.  
17  
18  
19

20 Our primary outcome will be the change between baseline and 12 months in the overall raw score in  
21 reciprocal socio-communicative interactions and repetitive and restrictive behaviours in line with the  
22 DSM-V [26,29].  
23  
24

25 Researchers will be trained to achieve recognized standards. Regular reliability meetings of all  
26 researchers will address any discrepant ratings to maintain researcher calibration.  
27  
28

### 29 **Secondary outcomes**

30  
31 **To assess social communication and interaction in the natural setting of parent-child interaction at**  
32 **home:**  
33

34 -*Brief Observation of Social Communication Change (BOSCC)*[30].  
35

36 **To assess dyadic communication in the natural setting of parent-child interaction at home:**  
37

38 -*Dyadic Communication Measure for Autism (DCMA)* [24].  
39

40 **To assess child cognitive development:**  
41

42 -*Mullen Scales of Early Learning (MSEL)* [23]  
43  
44

45 **To assess child language development:**  
46

47 -*Development of Expressive Language, (Development du Langage de Production In french\_DLPP)*[31].  
48  
49

50 **To assess Adaptative behavior of the child:**  
51

52 -*Vineland Adaptive Behaviour Scales second version (VABS-2)* [32]  
53  
54

55 **To assess Parent's Stress, health, priorities and experience of the family:**  
56

57 -*Autism Family Experience Questionnaire (AFEQ)* [33]  
58  
59

60 - *Parental Stress Index (PSI)* [34].



1  
2  
3 -General Health Questionnaire (GHQ-28) [35]  
4

5 **To assess implementation of the intervention:**  
6

7 - PACT Fidelity Rating Scale  
8

9 -Number of PACT training sessions undertaken  
10

11 -Quality of videoconferencing during each session  
12

13 -Parents acceptability of videoconferencing and implementation of PACT at home (self-report on  
14 Likert-scale)  
15

16 -Number of hours per day using PACT at home at 12 months  
17

18 -Parent's qualitative PACT adherence coded with DCMA on a 12-minute home child-parent interaction  
19 video  
20

21 Appendix 1 shows more details about assessments.  
22

23 Figure 2 shows schedule of enrolment, interventions and assessments.  
24

25 **Participants timeline**  
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The 'referent parent' to take part in the therapy trial will be decided before randomisation. Children will be subsequently randomised into the intervention or TAU group. Parents will be informed of the result of the randomisation and complete the assessment.

45 **Assignment of intervention**  
46

47 ***Allocation sequence generation and randomisation***  
48

49 All eligible toddlers, with parental consent, will be assigned to the two study groups in a 1:1 ratio using  
50 the minimization method with the following stratification factors: the centre, the children's age, level  
51 of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a  
52 minimization algorithm with a .90 random element will be used and known only by the statistician  
53 (AD). The randomisation is centralized.  
54  
55  
56

57 ***Blinding***  
58

59 Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation  
60 group. PACT therapists will not be involved in the diagnosis or assessment. An assessor blind to the

1  
2  
3 allocation group will administer every assessment. Data manager and biostatistician will be blinded to  
4 the allocation groups.  
5

## 6 **Data collection and management**

### 7 ***Data collection***

8  
9  
10 Data will be collected through standardized observations done by a researcher blind of the allocation  
11 and questionnaires and interviews completed by parents. We will be particularly vigilant about the  
12 measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.  
13  
14

### 15 ***Participation retention and follow-up***

16  
17 Children of both groups will benefit from early diagnosis and assessment and will have the same follow-  
18 up evaluations over the 1-year study period in the diagnostic units which should promote participant  
19 retention and complete follow-up. Any discontinuation of study participation will be collected and  
20 recorded with the reasons.  
21  
22

### 23 ***Data Management***

24  
25 The study data will be collected on a secure electronic case report form (eCRF) that will be available at  
26 each centre through an internet portal. No personal identifying information will be mentioned on the  
27 eCRF. Each subject included in the study will be assigned a unique identification number.  
28  
29

30 All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be  
31 secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing  
32 cabinet at each centre. Access to these files will be limited to research staff involved in the study.  
33  
34

35 The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.  
36

## 37 **Statistical analysis**

### 38 ***Simple size calculation***

39  
40  
41 On the basis of the findings of the PACT Trial (Green, 2010), we have powered the study to be able to  
42 detect a difference in change overall on the ADOS score of 2 points. The group difference in mean  
43 change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9,  
44 SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS  
45 restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-  
46 3.9, SD=4.7 in PACT+TAU group). The pre- and post-measures were correlated at 0.67. Therefore, the  
47 most conservative values were fixed for ADOS standard deviation and for correlation among the  
48 repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm)  
49 was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU  
50 compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-  
51 out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide  
52 about 80% power for the study.  
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### 60 ***Feasibility of recruitment***

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3 A strong partnership with ASD orientation platforms recently implemented in France, a broad  
4 communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational  
5 therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will  
6 allow the trial team to reach the sample size over 2 years.  
7  
8  
9

### 10 11 **Statistical analysis**

12  
13 A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will  
14 be reported at the 12-month endpoint in accordance with the CONSORT 2010 statement. No interim  
15 analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat  
16 principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).  
17  
18

19 Baseline characteristics will be presented in each group.  
20

21 Summary statistics will be presented for process variables (number of PACT sessions, quality of  
22 videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours  
23 declared to be realized with the child) to show the feasibility and acceptability of PACT implementation  
24 in the intervention group.  
25  
26

27 The pattern of missing data will be investigated (number and mechanism of missingness). Missing data  
28 strategies can be applied and sensitivity analysis of different strategies (simple or multiple imputation)  
29 will be conducted.  
30  
31

32 A repeated measures analysis will be used to test the effect of PACT intervention on overall ADOS  
33 module 1 score over the 12-month study period. A linear mixed model will be run with the overall  
34 ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or  
35 TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random  
36 effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-  
37 2) and gender) and baseline variables that showed evidence of treatment group imbalance. Time will  
38 be represented by dummy variable. Model assumption will be verified according to residual analysis.  
39 If most of assumptions are not met other alternative such as transformation for ADOS overall raw score  
40 can be examined. Sensitivity analyses like complete case and per-protocol analysis can be performed  
41 to assess the robustness of the results to protocol deviations. In complete case analysis, only patient  
42 with primary outcome documented will be analyzed. In per-protocol participants who violate the  
43 protocol will be excluded from the analysis.  
44  
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47

48 All the secondary outcomes, (overall total score of the BOSCC, communication initiation and synchrony  
49 measured with the DCMA, overall raw score of the MSEL in receptive and expressive language, overall  
50 score in expressive language of the DLFP, overall raw score of communicative and social of the VABS,  
51 Parental Stress Index, Parent General Health score, AFEQ score) will be analyzed in a similar way using  
52 when appropriate linear or generalized linear mixed models. Tobit models should be used to address  
53 potential floor effects.  
54  
55

56 We will finally explore the parent's and children's characteristics, moderating the implementation and  
57 efficacy of this therapy. We will also test the previously found mediators implicated in the efficacy of  
58 this therapy [14].  
59  
60

## Qualitative analysis of barriers and facilitators of implementation

Based on parents and of the therapists reports we will describe the facilitators and barriers of the implementation of video-conferencing PACT.

The data will be collected through semi-structured interview and will be analysed with the classical technique of Interpretative Phenomenological Analysis (IPA) [36]. Population selection will follow the rules of the purposive sampling and will allow a maximal variation of the sample [37]. An estimation of 30-60 parents will be necessary to reach data saturation based on previous studies [38–40]. The total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we will explore different area of barriers and obstacles to learning and implementing PACT by videoconferencing. A guide for the interview will be elaborated in the initial phase of the project based on first interviews. Interviews will be recorded, and the verbatim interview will be transcribed to analysis the entirely communication of the participant.

Data from the quantitative and qualitative sources in the process evaluation will be analysed separately. The results of the qualitative study will be integrated with the quantitative results to optimize the findings [41].

## Monitoring

Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent representatives and associate researcher composed the trial steering committee (TSC). The TSC is independent of sponsor and funders and have no competing interests. The TSC has developed the study protocol and is responsible for data collection, management, publications and the final data set.

The coordinating center is independent from the centers for investigation.

According to the French law, the study requires formal data monitoring undertaken by the sponsor. Annual reporting will be completed and submitted to the funders.

## Adverse events

Based on results from previous PACT intervention trials, no specific harm from trial participation is anticipated. However, as required by the French law, adverse events will be collected throughout the study and reported in the eCRF section. Description of the event, date of occurrence, intensity, severity, accountability will be reported. Outcomes of this event and action taken after its report will also be concealed.

We anticipate that the early assessment, follow-up consultation on ASD and its management will help and support both groups during the post-diagnosis period. Hence, no post-trial care is planned.

## Trial status

The trial status is currently Recruiting. The study has started the 30th June 30, 2020. The anticipated end date will be 30<sup>th</sup> June, 2023.

Figure 3 shows WHO trial registration data set.

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3 **Ethics and Dissemination:** This study is approved by the French Institutional Review Board (reference  
4 No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also  
5 disseminate via national and international, general and specialist meeting and through the parent  
6 association (<https://bleunetwork.fr>; <https://autisme-ambitionavenir.com>; [desailespourgrandir.org](https://desailespourgrandir.org)).  
7 An individual feedback to the participant will be done through a regular newsletter. We will adhere  
8 to defined authorship criteria as per the International Committee of Medical Journal Editors.  
9

10  
11 **Author contribution:** MMG and ST, PO, LJ conceived and designed the project, and MMG is leading  
12 the coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding.  
13 LJ and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ  
14 contributed to the sample size calculation, the randomisation procedure and the statistical plan, and  
15 are responsible for data management, randomisation and statistical analysis. JG contributed to the  
16 protocol and paper writing. ARL contributed to the protocol of the qualitative study. CA and NG to  
17 the PACT training and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible  
18 for recruitment and evaluation of children. SG contributed to draft the paper. All authors critically  
19 reviewed and approved the final version of the manuscript.  
20  
21

22  
23 **IFPAD Study group:** Mrs Pauline Auphan (psychologist), Mrs Laetitia Bouveret (research assistant),  
24 Mrs Laurie Herman (research assistant), Dr Anne-Laure Toureille (PACT trainer), Mrs Lucie Jansen  
25 (PACT trainer), Dr Sandrine Sonié (CRA Lyon), Pr. Mario Speranza (CHU Versaille), Pr. Bruno Falissard  
26 (Paris), Pr Nicolas Georgieff (Lyon), Dr Matias Winter (HCL), Mrs Nadège Alloisio (parent association),  
27 Mr Chams-Ddine BELKHAYAT (parent association).  
28  
29

30 **Patient and Public Involvement subsection:** Mrs Alloisio (Association AAA [https://autisme-](https://autisme-ambitionavenir.com)  
31 [ambitionavenir.com](https://autisme-ambitionavenir.com)) and Mr Belkhayat (association <https://bleunetwork.fr/pro>) are parents of a  
32 child with autism and represent two different association. They are part of the steering committee.  
33  
34

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36 Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by  
37 the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched  
38 for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national  
39 de la santé et de la recherche médicale (Inserm) ( IReSP-17-Autisme3-16).  
40  
41

42 **Disclaimer:** The funders and sponsor have no role in study design, data collection, management, data  
43 analysis and interpretation of data, in the writing of the report or in the decision to submit the  
44 manuscript for publication.  
45  
46

47 **Competing interests' statement:** None declared.  
48

49 **Consent:** Obtained from the both parents of the child.  
50  
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52 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
53

54 **Data sharing statement:** The trial statisticians will have access to the data set for the analysis of trial  
55 outcomes. The PI will have access to the data and will take full responsibility for the analysis and  
56 publication of the results. Once the main analyses have been undertaken, data will be available to  
57 principal and other investigator subject for approval of data analysis plans by the steering  
58 committee.  
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## References

- 1 Kogan MD, Vladutiu CJ, Schieve LA, *et al*. The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. *Pediatrics* 2018;**142**:e20174161. doi:10.1542/peds.2017-4161
- 2 Lyall K, Croen L, Daniels J, *et al*. The Changing Epidemiology of Autism Spectrum Disorders. *Annu Rev Public Health* 2017;**38**:81–102. doi:10.1146/annurev-publhealth-031816-044318
- 3 Baghdadli A, Miot S, Rattaz C, *et al*. Investigating the natural history and prognostic factors of ASD in children: the multicentric Longitudinal study of childrEN with ASD-the ELENA study protocol. *BMJ Open* 2019;**9**:e026286.
- 4 Howlin P. Living with impairment: The effects on children of having an autistic sibling. *Child: care, health and development* 1988;**14**:395–408.
- 5 HAS. Trouble du spectre de l'autisme Signes d'alerte, repérage, diagnostic et évaluation chez l'enfant et l'adolescent. 2018;:45.
- 6 Geoffroy M-M, Thevenet M, Georgieff N. News in early intervention in autism. *Psychiatr Danub* 2016;**28**:66–70.
- 7 Oono IP, Honey EJ, McConachie H. Parent-mediated early intervention for young children with autism spectrum disorders (ASD). *Evidence-Based Child Health: A Cochrane Review Journal* 2013;**8**:2380–479.
- 8 Zwaigenbaum L, Bauman ML, Choueiri R, *et al*. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics* 2015;**136**:S60–81.
- 9 French L, Kennedy EMM. Annual Research Review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: a systematic review. *J Child Psychol Psychiatry* 2018;**59**:444–56. doi:10.1111/jcpp.12828
- 10 Sandbank M, Bottema-Beutel K, Crowley S, *et al*. Project AIM: Autism intervention meta-analysis for studies of young children. *Psychological Bulletin* 2020;**146**:1–29. doi:10.1037/bul0000215
- 11 Green J, Garg S. Annual Research Review: The state of autism intervention science: progress, target psychological and biological mechanisms and future prospects. *Journal of Child Psychology and Psychiatry* 2018;:424–43. doi:10.1111/jcpp.12892@10.1111/(ISSN)1469-7610.Jack\_Tizard\_VI\_Autism\_Learning\_Disabilities
- 12 Green J, Charman T, McConachie H, *et al*. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. *The Lancet* 2010;**375**:2152–60.
- 13 Pickles A, Le Couteur A, Leadbitter K, *et al*. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet* 2016;**388**:2501–9. doi:10.1016/S0140-6736(16)31229-6



- 1  
2  
3 14 Pickles A, Harris V, Green J, *et al.* Treatment mechanism in the MRC preschool autism  
4 communication trial: implications for study design and parent-focussed therapy for children. *J Child*  
5 *Psychol Psychiatry* 2015;**56**:162–70. doi:10.1111/jcpp.12291  
6  
7  
8 15 Vismara LA, McCormick CEB, Wagner AL, *et al.* Telehealth Parent Training in the Early Start  
9 Denver Model: Results From a Randomized Controlled Study. *Focus Autism Other Dev Disabl*  
10 2018;**33**:67–79. doi:10.1177/1088357616651064  
11  
12 16 Vismara LA, McCormick C, Young GS, *et al.* Preliminary Findings of a Telehealth Approach to  
13 Parent Training in Autism. *J Autism Dev Disord* 2013;**43**:2953–69. doi:10.1007/s10803-013-1841-8  
14  
15 17 Green J, Aldred C, Charman T, *et al.* Paediatric Autism Communication Therapy-Generalised  
16 (PACT-G) against treatment as usual for reducing symptom severity in young children with autism  
17 spectrum disorder: study protocol for a randomised controlled trial. *Trials* 2018;**19**:514.  
18 doi:10.1186/s13063-018-2881-3  
19  
20 18 Khan K, Hall CL, Davies EB, *et al.* The Effectiveness of Web-Based Interventions Delivered to  
21 Children and Young People With Neurodevelopmental Disorders: Systematic Review and Meta-  
22 Analysis. *J Med Internet Res* 2019;**21**:e13478. doi:10.2196/13478  
23  
24 19 Bearss K, Burrell TL, Challa SA, *et al.* Feasibility of Parent Training via Telehealth for Children  
25 with Autism Spectrum Disorder and Disruptive Behavior: A Demonstration Pilot. *J Autism Dev Disord*  
26 2018;**48**:1020–30. doi:10.1007/s10803-017-3363-2  
27  
28 20 Richards DA, Bazeley P, Borglin G, *et al.* Integrating quantitative and qualitative data and  
29 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
30 doi:10.1136/bmjopen-2019-032081  
31  
32 21 Feters MD, Curry LA, Creswell JW. Achieving Integration in Mixed Methods Designs-  
33 Principles and Practices. *Health Serv Res* 2013;**48**:2134–56. doi:10.1111/1475-6773.12117  
34  
35 22 Kim SH, Thurm A, Shumway S, *et al.* Multisite Study of New Autism Diagnostic Interview-  
36 Revised (ADI-R) Algorithms for Toddlers and Young Preschoolers. *J Autism Dev Disord* 2013;**43**:1527–  
37 38. doi:10.1007/s10803-012-1696-4  
38  
39 23 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.  
40  
41 24 Aldred C, Green J, Emsley R, *et al.* Brief report: Mediation of treatment effect in a  
42 communication intervention for pre-school children with autism. *Journal of autism and*  
43 *developmental disorders* 2012;**42**:447–54.  
44  
45 25 Dunn G, Emsley R, Liu H, *et al.* Evaluation and validation of social and psychological markers  
46 in randomised trials of complex interventions in mental health: a methodological research  
47 programme. *Health Technology Assessment* 2015;**19**. doi:10.3310/hta19930  
48  
49 26 Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism  
50 spectrum disorders. *Journal of autism and developmental disorders* 2009;**39**:693–705.  
51  
52 27 Lord C, Risi S, Lambrecht L, *et al.* The autism diagnostic observation schedule-generic: a  
53 standard measure of social and communication deficits associated with the spectrum of autism. *J*  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 *Autism Dev Disord* 2000;**30**:205–23.  
4

5 28 McConachie H, Parr JR, Glod M, *et al.* Systematic review of tools to measure outcomes for  
6 young children with autism spectrum disorder. *Health Technology Assessment* 2015;**19**:1–506.  
7 doi:10.3310/hta19410  
8

9  
10 29 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th*  
11 *ed.)*. Washington, DC. 2013.  
12

13 30 Grzadzinski R, Carr T, Colombi C, *et al.* Measuring Changes in Social Communication  
14 Behaviors: Preliminary Development of the Brief Observation of Social Communication Change  
15 (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9  
16

17  
18 31 Bassano D, Labrell F, Bonnet P. Le Développement du langage de production en français  
19 (DLPF) entre 18 et 42 mois : une synthèse. *Enfance* 2020;**N°2**:151. doi:10.3917/enf2.202.0151  
20

21 32 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS Pearson  
22 2005.  
23

24  
25 33 Leadbitter K, Aldred C, McConachie H, *et al.* The Autism Family Experience Questionnaire  
26 (AFEQ): An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life and  
27 Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62.  
28 doi:10.1007/s10803-017-3350-7  
29

30  
31 34 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire :  
32 validation et normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier  
33 et Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar  
34

35 35 Pariente P, Challita H, Mesbah M, *et al.* The GHQ-28 questionnaire in French : a validation  
36 survey in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.  
37

38  
39 36 Smith JA, Shinebourne P. Interpretative phenomenological analysis. In: Cooper H, Camic PM,  
40 Long DL, *et al.*, eds. *APA handbook of research methods in psychology, Vol 2: Research designs:*  
41 *Quantitative, qualitative, neuropsychological, and biological*. Washington: : American Psychological  
42 Association 2012. 73–82. doi:10.1037/13620-005  
43

44  
45 37 Guba EG, Lincoln. *Fourth generation evaluation*. Sage Publications, Inc. 1989.  
46

47 38 Lachal J, Speranza M, Taïeb O, *et al.* Qualitative research using photo-elicitation to explore  
48 the role of food in family relationships among obese adolescents. *Appetite* 2012;**58**:1099–105.  
49 doi:10.1016/j.appet.2012.02.045  
50

51 39 Gorse P, Nordon C, Rouillon F, *et al.* Subjective Motives for Requesting In-Patient Treatment  
52 in Female with Anorexia Nervosa: A Qualitative Study. *PLoS ONE* 2013;**8**:e77757.  
53 doi:10.1371/journal.pone.0077757  
54

55  
56 40 Morse JM. The Significance of Saturation. *Qual Health Res* 1995;**5**:147–9.  
57 doi:10.1177/104973239500500201  
58

59  
60 41 Richards DA, Bazeley P, Borglin G, *et al.* Integrating quantitative and qualitative data and

1  
2  
3 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
4 doi:10.1136/bmjopen-2019-032081  
5  
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11  
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For peer review only

Figure 1 Consort flow-chart of the study.

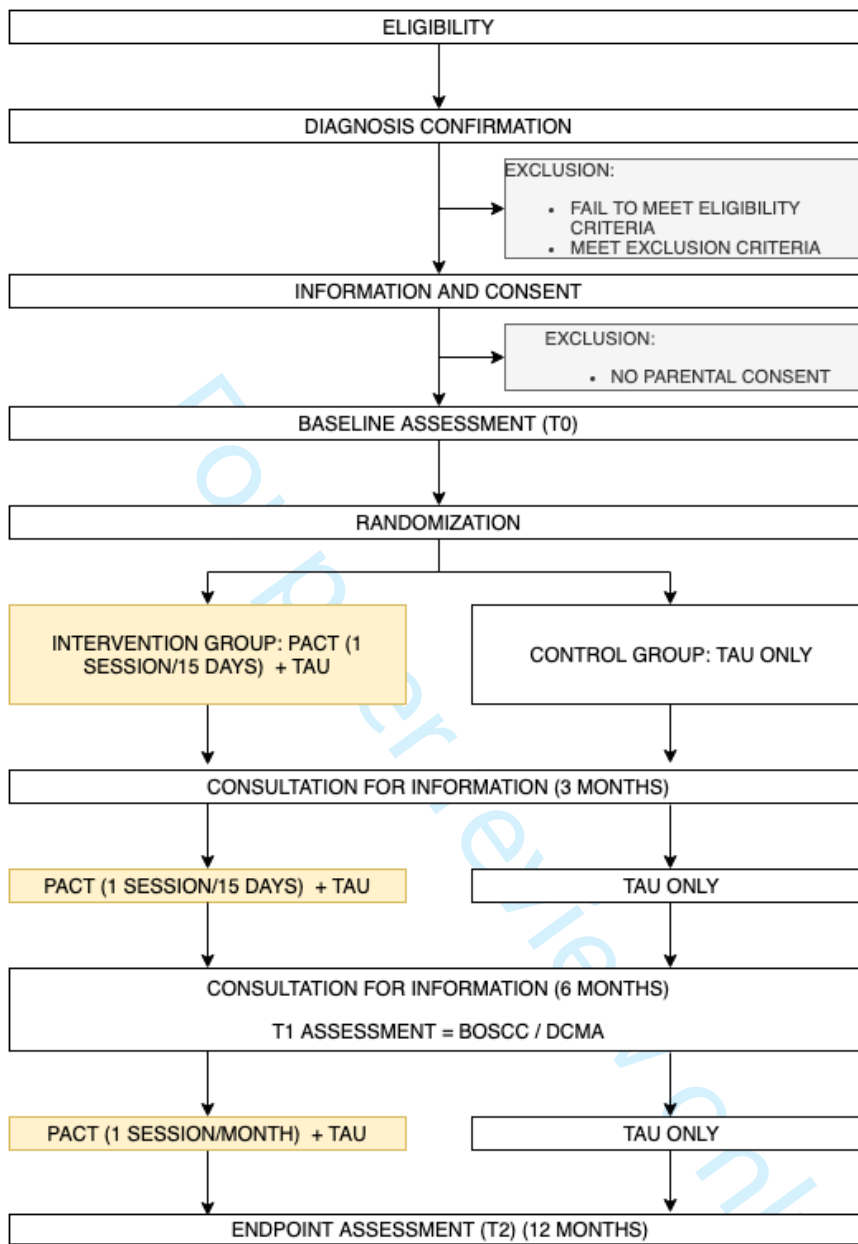


Figure 2. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	Enrolment	T0 baseline	T1 6 months	T2 12 months
<b>Eligibility screen</b>				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
<b>Intervention</b>				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home			—————→	
Treatment as usual			—————→	
<b>Assessment</b>				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
<b>Implementation:</b>				
Number of PACT training session				x
Mean of quality of videoconferencing collected after each session				x
Number of hours declared by parents using PACT at home				x

Figure 3- WHO trial registration data set

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) ( IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
Contact for public queries	Marie-Maude Geoffray (PI), email: marie-maude.geoffray @ch-le-vinatier.fr Lucie Jurek, email : lucie.jurek@ch-le-vinatier.fr Pauline Occelli, email: pauline.occelli@chu-lyon.fr
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Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recruitment	France
Health condition or problem studied	Autism spectrum disorder (ASD)

Data category	Information
Interventions	<p><i>Intervention:</i> PACT for toddlers and young children with ASD</p> <p><i>Description:</i> PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months.</p> <p><i>Control:</i> care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.</p>
Key inclusion and exclusion criteria	<p><i>Age:</i> between 18 and 36 months</p> <p><i>Sex:</i> male or female</p> <p><i>Inclusion criteria:</i> diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center.</p> <p><i>Exclusion criteria:</i> serious neurological or physical condition, family unavailable for a regular follow-up.</p>
Study type	<p>Interventional</p> <p><i>Allocation:</i> randomized 1:1; parallel assignment; blinding: assessor blind</p>
Date of first enrolment	15th July 2020
Target sample size	238
Recruitment Status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.

## Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

### To assess social communication and interaction in the natural setting of parent-child interaction at home

*Brief Observation of Social Communication Change (BOSCC)* measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

### To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).



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3 Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated  
4 and retro-translated for the purpose of a previous study [2]  
5

6 It can be used to code a number of acts of communication per timepoint. A higher score indicates  
7 better communication.  
8

9  
10 Coding will be done on the same 12 minutes home parent-child video described above in BOSCC at  
11 baseline, 6 months and 12 months.  
12

### 13 **To assess child cognitive development**

14  
15 The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68  
16 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure  
17 in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively  
18 as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X  
19 syndrome, and speech delays [5–7]  
20  
21

22 The MSEL will be assessed on the center before the inclusion and at 12 months.  
23

24 Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for  
25 the purpose of a previous study [2]  
26  
27

28 The MSEL includes 124 items that measure five specific domains: 1) Gross Motor; 2) Fine  
29 Motor; 3) Visual Reception; 4) Expressive Language; and 5) Receptive Language. Scoring varies  
30 by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point scale. Results  
31 for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age equivalents.  
32 Four cognitive scales (Visual Reception, Fine Motor, Receptive Language, and Expressive  
33 Language) sum to represent an Early Learning Composite Score which measures overall  
34 cognitive functioning (M=100, SD=15). A higher score means better skills. This evaluation will be  
35 realized before inclusion and at 12 months.  
36  
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### 39 **To assess child language development**

40  
41 The “development of expressive language”, a standardised French Scale (Development du Language  
42 de Production In french\_DLPF), is based on a self-administered parent-report [8]. This measure is  
43 standardised for age. Only the level 4 of the DLFP will be administered at each assessment to have a  
44 continuous score on expressive language. The DLFP was validated in a study [3]. Score is calculated  
45 based on the number of words in the naturalistic environment of the child as reported by the parents.  
46 A higher score means better language skills. This questionnaire will be completed by the referent  
47 parent at baseline and at 12 months.  
48  
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50 It will complete the measure of functional communication with VABS-2 and standardised measure with  
51 MSEL.  
52  
53

### 54 **Adaptative behavior**

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56 Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the  
57 child’s daily personal and social skills [9]. This measure will be collected via a parental interview over  
58 videoconferencing before the inclusion and at 12 months. Videoconferencing model has been chosen  
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3 in our study to avoid multiples visits on the centre but also to evaluate, before the inclusion, if a long  
4 videoconferencing meeting could be done with the family on a technical point of view. A first  
5 assessment will be proposed to the parents. In case of technical difficulties during the first meeting, a  
6 second, and if necessary, a third meeting will be proposed. Tips to improve videoconferencing will also  
7 be provided to the parents. In case of failure of every remote assessment, the family will be considered  
8 as not eligible for the study as the remote PACT session require the ability to conduct a  
9 videoconferencing meeting.  
10  
11

12  
13 This measure will provide an estimate of any assesses functional change in socialization,  
14 communication, motor and daily living skills, based on parent observation in the naturalistic settings  
15 of the child.  
16

17  
18 The VABS has well-established psychometric properties [9,10]. It is validated in french.  
19

20  
21 All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to  
22 '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score  
23 is described by normalized score (M=100, SD=15). The range for each subscale is from 20 to 140. The  
24 subscales are summed to compute a total score, ranging from 80 to 560. The higher the scores are, the  
25 better adaptive functioning the children achieve.  
26

### 27 28 **To assess Parent's Stress, health, priorities and experience of the family**

29  
30 The psychometry of the following tools are described in the manual of each tool.  
31

32  
33 *Autism Family Experience (AFEQ)* [11] is a 48-item self-administered parent report about quality of life  
34 and priorities for early intervention. It is composed of 4 subscales: experience of being a parent (range  
35 13-65), family life (range 9-45), child development understanding and relationships (14-70), child  
36 symptoms (12-60). The sum of all domains gives the total score (range 48 - 240). Each question is  
37 assessed using a 5-point Likert scale. Scores range from "always" (1) to "never" (5)". It was translated  
38 and retro-translated for the purpose of this study with the author. For the total score and the domain  
39 scores a higher score indicates a lower outcome. This questionnaire will be completed by the referent  
40 parent at baseline and at 12 months.  
41  
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43  
44 *ISP (Parental stress index)* is a 36-item self-administered parent report to measure the stress in the  
45 parent-child system. The PSI consists of three subscales: Parental Distress, Parent-child Dysfunction  
46 Interaction, and Difficult Child. Each subscale consists of 12 items rated from 1 (strongly agree) to 5  
47 (strongly disagree), with subscale scores ranging from 12 to 60. The three domains combined form a  
48 Total Stress score (with a total score ranges from 36 to 180). We will use the short form of the 4th  
49 edition. A validated French version exists [12]. A higher score on the subscales and total stress score  
50 indicates increased levels of stress. This questionnaire will be completed by the referent parent at  
51 baseline and at 12 months.  
52  
53

54  
55 *General Health Questionnaire (GHQ-28)* is a self-administered parent report, 28 item scaled version,  
56 assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. Each  
57 item is rated according to a Likert score method (1 to 4). The GHQ-28 global score range from 36 to  
58 110 [13]. A higher score means more health problems. This questionnaire will be completed by the  
59 referent parent at baseline and at 12 months.  
60

## To assess implementation of the intervention

### *Professional adherence to the treatment:*

All therapy training sessions with professionals will be videotaped and will be independently rated by the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual including the style of training.

### *Acceptability and feasibility of the PACT session*

The therapist will collect the number of the session done with each parent. The quality of videoconferencing during each session with the professional will be rated. Quality of sound and quality of the image will be rated with a 4-points Likert scale. The number of disconnections along the session will also be collected.

The parents will self-report (likert-scale) the acceptability of videoconferencing training and implementation of PACT at home.

### *Parent PACT adherence at home*

At 12 months, Parents will declare the average number of hours per day using PACT at home outside the PACT session with the therapist.

DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative adherence of PACT intervention.

- 1 Grzadzinski R, Carr T, Colombi C, *et al.* Measuring Changes in Social Communication Behaviors: Preliminary Development of the Brief Observation of Social Communication Change (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9
- 2 Touzet S, Ocelli P, Schröder C, *et al.* Impact of the Early Start Denver Model on the cognitive level of children with autism spectrum disorder: study protocol for a randomised controlled trial using a two-stage Zelen design. *BMJ open* 2017;**7**:e014730.
- 3 Aldred C, Green J, Emsley R, *et al.* Brief report: Mediation of treatment effect in a communication intervention for pre-school children with autism. *Journal of autism and developmental disorders* 2012;**42**:447–454.
- 4 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.
- 5 Burns TG, King TZ, Spencer KS. Mullen Scales of Early Learning: The Utility in Assessing Children Diagnosed With Autism Spectrum Disorders, Cerebral Palsy, and Epilepsy. *Applied Neuropsychology: Child* 2013;**2**:33–42. doi:10.1080/21622965.2012.682852
- 6 Bishop SL, Guthrie W, Coffing M, *et al.* Convergent validity of the Mullen Scales of Early Learning and the differential ability scales in children with autism spectrum disorders. *American journal on intellectual and developmental disabilities* 2011;**116**:331–343.
- 7 Farmer C, Golden C, Thurm A. Concurrent validity of the differential ability scales, second edition with the Mullen Scales of Early Learning in young children with and without neurodevelopmental disorders. *Child Neuropsychology* 2016;**22**:556–69. doi:10.1080/09297049.2015.1020775

- 1  
2  
3 8 Bassano D, Labrell F, Champaud C, *et al.* Le DLPPF : un nouvel outil pour l'évaluation du  
4 développement du langage de production en français. *Enfance* 2005;**57**:171.  
5 doi:10.3917/enf.572.0171  
6  
7 9 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS Pearson 2005.  
8  
9 10 Chatham CH, Taylor KI, Charman T, *et al.* Adaptive behavior in autism: Minimal clinically important  
10 differences on the Vineland-II: Adaptive behavior and autism. *Autism Research* 2018;**11**:270–83.  
11 doi:10.1002/aur.1874  
12  
13 11 Leadbitter K, Aldred C, McConachie H, *et al.* The Autism Family Experience Questionnaire (AFEQ):  
14 An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life and  
15 Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62.  
16 doi:10.1007/s10803-017-3350-7  
17  
18 12 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire : validation et  
19 normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier et  
20 Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar  
21  
22 13 Pariente P, Challita H, Mesbah M, *et al.* The GHQ-28 questionnaire in French : a validation survey  
23 in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.  
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# BMJ Open

## Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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# Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol

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## Abstract

**Introduction:** Intervention in the preschool period is currently recommended for Autism Spectrum Disorder (ASD). Therapies delivered by parents are particularly suitable for young children. PACT (Preschool Autism Communication Trial) is a parent-mediated therapy that has shown a significant and sustained impact on autism symptom reduction. However, access to such evidence-based therapies for families is limited due to autism centers located in large urban areas. Using videoconferencing to deliver PACT training to parents may improve accessibility for families living in underserved areas.

**Methods and analysis:** This single-blind randomized controlled trial, involving six sites in France, will investigate the efficacy of a telehealth, videoconferencing-based, parent-mediated PACT therapy on autism symptoms, over a 12-month period. It will compare PACT plus treatment as usual (TAU) against TAU only in a cohort of 238 toddlers (119 per group) aged 18 to 36 months at inclusion and living with their families more than 40 minutes away from the specialist centres for autism. Primary outcome will include change of overall autism score on the Autism Diagnostic Observation Scale (ADOS) at 12 months. Secondary outcomes will measure change in child skills, child functioning, impact on parents (stress, health, priorities) and implementation characteristics.

Repeated measures analyses will be used to test the effect of PACT intervention on the overall ADOS module 1 score over the 12-month study period. Linear mixed models will be used with time, treatment allocation and the interaction between treatment and time as fixed effects and individual variation as random effect.

**Ethics and dissemination:** This protocol (version N°5, date: 10/25/2019) is approved by the French National Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals

## Article Summary

### Strengths and limitations of this study

- Large multicentre randomised controlled trial (RCT) in children with ASD under 3 years old, testing remote delivery of an evidenced intervention
- Assessment partially done by videoconferencing and based on video material sent by parents
- Recruitment targeted to children living in underserved areas
- Short term effect of the intervention will be assessed at 12 months (end of the intervention)
- Owing to the nature of the intervention, parents of the children and PACT therapists will not be blind to the allocation group.

**Keys Words:** Early intervention, Autism spectrum Disorder, PACT, videoconferencing, parent-mediated therapy, video-feedback, Health Services Accessibility

**Trial registration:** ClinicalTrials.gov Identifier: NCT04244721

## Introduction

### Rationale & background

Autism Spectrum disorder (ASD) is a common neurodevelopmental disorder with a population prevalence of at least 1.5% in developed countries and can cause significant lifelong disability [1–3] and burden for families and caregivers [4]. Diagnosis is possible as early as 18 months of age [5]. Current evidence suggests that interventions delivered in the early developmental period before the age of 3 years has the potential for maximal impact on autism symptom severity.

Therapies can be delivered by therapists, teachers and parents [6]. For preschool children with ASD, parent-mediated therapies can guide parents to face challenging social interaction with their children [7,8]. Among the different parent-mediated therapies, PACT (Pre-school Autism Communication Therapy) has shown significant short and long-term efficacy on objectively assessed autism symptoms in children aged from 2 to 10 years in a large UK cohort (N=152); as showed in a recent systematic review [9] and meta-analysis [10]. In PACT, parents are guided by a therapist via video feedback to optimize parent-child dyadic interaction, which in turn impacts on child language, communication and autism symptoms [11]. In a trial of PACT intervention compared to regular care, PACT showed a statistically significant effect at 13 month endpoint to reduce of autism symptom severity measured on Autism diagnostic Observation Schedule version 2 (ADOS-2) (effect size 0.64; 95%CI 0.07-1.20); and an increase in parental communication synchrony with the child and child communication initiations with the parent [12]. The follow-up study showed evidence of sustained effect on autism symptom severity six years after intervention end, with a significant overall reduction in symptom severity over the course of trial and follow-up period (effect size=0.55, 95% CI 0.14 to 0.91, p=0.004)[13]. A mechanistic study also confirmed that the distal effect of PACT therapy on autism severity measured by ADOS was mediated by the improvement of child communication initiations, which in turn was mediated by improved parent-child synchrony [14].

Availability of PACT therapy is limited; even more so in rural settings or in regions away from specialist centres. Using videoconferencing run by therapists to train parents in PACT, may therefore be a viable alternative to make such therapies available to families living far from autism centers. Previous studies have shown that it is possible to provide parent-mediated therapies in autism by videoconferencing successfully [15,16]. The team who developed the PACT therapy reported positive experiences of parent guidance by videoconferencing (C. Aldred and J. Green, personal communication, June 10, 2020). Indeed, videoconferencing was used to deliver some of the PACT sessions in a recently published RCT [17]. However, PACT has never been evaluated when exclusively delivered by videoconferencing. The barriers and facilitators to delivering such therapies via videoconferencing are not sufficiently well understood, and hence it is essential to investigate and address them adequately [18,19].

Research question: The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness on autistic symptom severity and other measures of PACT therapy delivered to parents by videoconferencing.

A significant effect would justify and facilitate the routine use of videoconferencing therapy in early intervention and improve the dissemination of this evidence-based practice.

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2  
3 The hypothesis is that PACT intervention delivered by videoconferencing + TAU (Treatment As Usual)  
4 will have a superior efficacy on child autism symptom severity as compared to TAU alone.  
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## 9 **Objectives**

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11 Our primary objective will be to test the efficacy of a parent-mediated PACT therapy, delivered by  
12 trained therapists to parents living in underserved areas via videoconferencing over a 12-months  
13 period, on overall autistic symptoms in children with ASD aged from 18 to 36 months at inclusion,  
14 measured using the Autism Diagnostic Observation Schedule 2 (ADOS),  
15  
16

17 Our secondary objectives will include an evaluation of change in child socio-communicative  
18 interactions, language, communication initiation and daily adaptive behaviour. At the parent level, we  
19 will evaluate the intervention effects on stress, health and family functioning.  
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22 The implementation of the therapy will be evaluated through the adherence of professionals and  
23 parents to PACT, and acceptability and feasibility of the PACT sessions to parents and therapists.  
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## 28 **Method**

### 29 **Study design**

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31 This is a prospective multicentre RCT with 2 parallel group, 1:1 ratio, single blind comparing PACT  
32 intervention + Treatment As Usual (TAU) against TAU alone. Evaluation will be carried out using  
33 quantitative and qualitative mixed-method approaches [20,21].  
34  
35  
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37

38 Semi-structured interviews with parents and therapists will be conducted to understand the barriers  
39 and facilitators of using the videoconferencing approaches to delivering the PACT therapy.  
40  
41

42 Figure 1 shows consort flow-chart of the study.  
43

### 44 **Setting**

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46 We will run this trial in six academic centres located in child and adolescent public hospitals in France.  
47 All centres have a unit for ASD diagnosis and assessment and a distinct unit for intervention where  
48 therapists have been trained in PACT and can provide PACT via videoconferencing. The parents  
49 receiving intervention come from a French-speaking population including socioeconomically  
50 disadvantaged groups.  
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### 56 **Patient and Public Involvement**

57  
58 Mrs Alloisio (Association AAA <https://autisme-ambitionavenir.com>) and Mr Belkhat (association  
59 <https://bleunetwork.fr/pro>) are parents of a child with autism and represent two different  
60 association. They are part of the steering committee.

## Population

### *Inclusion criteria*

Children will be included if they meet the following criteria:

- i) aged between 18-36 months old at referral
- ii) meet criteria for autism spectrum disorder using the two gold standard instruments ADOS-2 (Autism diagnostic Observation Schedule -2) and ADI-R (Autism Diagnostic Interview-Revised). For inclusion into the study, the severity score comparison (CSS) on ADOS-2 will be greater or equal to 4. The score on the ADI-R algorithm for toddlers will be greater or equal to 11 [22]. The diagnosis will be confirmed by a multidisciplinary team trained in ASD assessment and diagnoses based in the academic departments of the hospitals.
- iii) have a non-verbal age equal to or above 12 months on the Mullen Scale of Early learning ( MSEL) [23].
- iv) live more than 40 minutes away from a Center for Resources in Autism (regional center)

Referred parents will be included if they meet the following criteria:

- ii) speak French with their children
- iii) are able to use videoconferencing methods with therapists who will be based at the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing) (see Appendix 1 for details)

### *Exclusion criteria*

Exclusion criteria for the child will include:

- i) a twin brother or sister with ASD or a brother or sister already included in the study
- ii) diagnosed with epilepsy requiring medication
- iii) severe hearing or visual impairment
- iv) an identification of a genetic anomaly which may impact on their ability to participate in the intervention or on data validity (determined by the principal investigator on a case-by-case basis).

Exclusion criteria for the referred parents (at least one parent with) will include:

- i) severe hearing or visual impairment
- ii) severe psychiatric disorder
- iii) unstable somatic disorders preventing participation in the intervention
- iv) lack of internet provision
- v) not available for regular intervention and follow-up
- vi) opposition of one parent to the child's participation in the study
- vii) currently undertaking PACT therapy

## **Intervention conducted in the experimental group**

### ***Eligibility criteria for PACT therapist and adherence***

Therapists delivering the intervention will include speech language pathologists, occupational therapists, clinical nurses, psychologists or child and adolescent psychiatrists, all specialised in ASD. The therapists have already received formal training and supervision in PACT from the team who developed this training [12,24]. Fidelity to PACT therapy will be maintained by regular meetings between therapists of all centers, with scoring and feedback of videotaped therapy sessions obtained during the study.

### ***PACT treatment principles***

As previously described [17], parents will be trained, via video-feedback, to identify and set key strategies facilitating the socio-communicative interactions between their child and themselves. Parents will also be encouraged to use PACT every day outside the training session at least half an hour a day. The therapy follows a six-staged approach based on child developmental progression and strategies for establishing fundamental skills for the socio-communicative development. The first two stages aim to increase parent's identification of child focus and interest, synchrony, responsiveness and sensitivity to the child interest and communication. The third and fourth stages are targeted towards developing expression and comprehension of the child by commenting and modelling language adapted to the child's developmental level. Child communication initiation is also improved in the fifth stage through different strategies such as anticipation and routine. The last stage aims to develop conversation and expansion of language for verbal children. Progression from one stage to the next depends on predefined criteria.

Based on the protocol of the first PACT RCT, parents will receive 18 sessions of training in PACT with the therapist over the 12 months [12,13]: 1-hour session every fortnight for the first 6 months to learn PACT strategies followed by 1 hour session per month over the next 6 months to maintain the capacity of parents to deliver the strategies.

Therapist will train only one parent per family and maintain fidelity to the therapy manual. The "referent parent" will have to be designated before the randomisation of the child. If the referent becomes unavailable, the therapy will stop or will continue with the other parent if possible and this change will be reported.

### ***Parent training session with the professional via videoconferencing***

Before each session, the parent will be asked to send a 10-minute video of their interaction with their child to the therapist via a secure cloud link. During the videoconferencing session (as in face-to-face intervention), referent parent will begin with a 5-minute discussion about their progress since the last session. The therapist will then share his/her screen and watch the home-based 10 minutes video together with the parent. Together the parent and therapist will identify, review and discuss specific clips that demonstrate accomplishment of therapy goals for the relevant stage of the PACT programme. The therapist's role will be to guide parents to identify successful strategies and responses (i.e. episodes of engagement and/ or mutual sharing with their child). Parents will be supported to reflect on their role in enhancing interaction and to identify new intervention goals.

### ***Parent PACT implementation in daily life outside the therapy session***

At the end of each session, the therapist will support the parent in setting 2-3 new goals, based on the strategies identified during the session. The therapist will encourage the parent to practice the strategies for the next session and discuss opportunities to achieve these goals in daily routine at home for at least 30 minutes per day. Parents will be guided to embed PACT strategies in everyday routines across different contexts. As therapy progresses, parents will be asked to send 10-minutes home videos of daily routines in different contexts.

### **Treatment as usual (TAU) and 2 follow-up consultations on ASD and its management**

Regardless of group allocation, parents will receive treatment as usual (TAU) consisting of psychoeducation about ASD, management and educational support for nursery and preschool placement. Parents will be referred to any relevant care available in the community (e.g.: Speech language pathologist (SLP), occupational therapist, educator, behavioural psychologist, psychiatrist). TAU received during the course of the study will be described in both groups.

Regardless of group allocation, a psychiatrist or a psychologist from each autism center will provide two supplementary 45 minutes follow-up consultations conducted by videoconferencing at 3 and 6 months after inclusion. This consultation will be carried out by following an interview guide. Three thematic areas will be systematically discussed with the parents: ASD information, access to treatment in the community, support for school or nursery. These follow-up consultations will ensure that parents of both groups receive homogeneous information on ASD and its management.

### **Avoidance of contamination**

Currently, PACT is not widely implemented in the community in France, particularly in the rural areas. Any families who are currently in receipt of PACT intervention will be excluded from this trial. However, any PACT that might be received in the community as part of TAU will be recorded .[25].

Research assessors will be separate to the therapists and will be located and supervised separately in each center.

Professionals conducting the follow-up consultations will not be trained in PACT therapy or be part of the research assessments.

### **Measures**

#### ***Primary outcome***

#### **To assess autism severity**

Autism Diagnostic Observation Schedule (ADOS-2) is a semi-structured, researcher-child interaction based, standardized observational assessment, in communication, play, imaginative skills, and repetitive behaviours [26,27]. It is a widely used scale in the field of ASD research with good



1  
2  
3 psychometric properties, recommended for the diagnosis of ASD and assessment of core autistic  
4 symptoms [28].  
5

6 At baseline and follow-up assessment after 12 months, we will use only ADOS-2 module 1, for children  
7 who are 18 months of age and older children who use no or few words.  
8

9  
10 There is a good Interrater reliability for Module 1 [27]. Internal consistency Cronbach's alpha  
11 coefficients was high in original study [27]. This scale has also shown that it can measure change in  
12 autism severity [13,28].  
13

14 ADOS-2 is composed of different items scored 0 to 3 or 0 to 2. Item A1 codes the level of language,  
15 from the severity for 'the child is using regular use of statements with two or more words' (code 0) to  
16 'the child has no spontaneous use of approximate words or words' (code 4). For children with no or  
17 limited language ( $A1 \geq 3$ ), the two items measuring language in the algorithm (item A3 speech  
18 abnormalities, item A5 stereotyped language) will be scored 3 (worst value) (see Green et al. 2010  
19 [12]). The minimum overall ADOS-2 module 1 raw score will be 0 and the maximum score 42. A higher  
20 score means more autistic symptoms.  
21  
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23  
24 Our primary outcome will be the change between baseline and 12 months in the overall raw score in  
25 reciprocal socio-communicative interactions and repetitive and restrictive behaviours in line with the  
26 DSM-V [26,29]  
27

28  
29 Researchers will be trained to achieve recognized standards. Regular reliability meetings of all  
30 researchers will address any discrepant ratings to maintain researcher calibration.  
31

### 32 **Secondary outcomes**

33  
34 **To assess social communication and interaction in the natural setting of parent-child interaction at**  
35 **home:**  
36

37 -*Brief Observation of Social Communication Change (BOSCC)*[30].  
38

39  
40 **To assess dyadic communication in the natural setting of parent-child interaction at home:**

41  
42 -*Dyadic Communication Measure for Autism (DCMA)* [24].  
43

44 **To assess child cognitive development:**

45  
46 -*Mullen Scales of Early Learning (MSEL)* [23]  
47

48 **To assess child language development:**

49  
50 -*Development of Expressive Language, (Development du Language de Production In french\_DLPF)*[31].  
51

52 **To assess Adaptive behavior of the child:**

53  
54 -*Vineland Adaptive Behaviour Scales second version (VABS-2)* [32]  
55

56  
57 **To assess Parent's Stress, health, priorities and experience of the family:**

58  
59 -*Autism Family Experience Questionnaire (AFEQ)* [33]  
60

1  
2  
3 - *Parental Stress Index (PSI)* [34].  
4

5 -*General Health Questionnaire (GHQ-28)* [35]  
6

7  
8 **To assess implementation of the intervention:**  
9

10 - *PACT Fidelity Rating Scale*

11  
12 -Number of PACT training sessions undertaken

13  
14 -Quality of videoconferencing during each session

15  
16 -Parent's acceptability of videoconferencing and implementation of PACT at home (self-report on  
17 Likert-scale)

18  
19 -Number of hours per day using PACT at home at 12 months

20  
21 -Parent's qualitative PACT adherence coded with DCMA on a 12-minute home child-parent interaction  
22 video  
23

24  
25 Figure 2 shows schedule of enrolment, interventions and assessments. Appendix 1 shows more  
26 detailed about assessment.  
27

28  
29 **Participant's timeline**  
30

31 Toddlers with a suspected ASD will be approached by health professionals with information about  
32 this study. The research recruitment team will meet with the family, complete the ADI-R during the  
33 first meeting, and confirm eligibility criteria. Complementary assessments, including ADOS, MSEL  
34 with the child and Vineland will be conducted by videoconferencing with the parent, to assess the  
35 criteria for eligibility. If toddlers and families meet the criteria for participation, parents will be  
36 informed about the study and possibility of an intervention using PACT or TAU based on  
37 randomisation. A written informed consent will be obtained if the parent/family agrees to participate  
38 in the study after one week of reflection (See Consent form in Appendix 2).  
39  
40

41  
42 The 'referent parent' used to refer to the parents who will engage with the PACT therapy will be  
43 decided before randomisation. Children will be subsequently randomised into the intervention or TAU  
44 group. Parents will be informed of the result of the randomisation  
45  
46

47 **Assignment of intervention**  
48

49 ***Allocation sequence generation and randomisation***  
50

51 All eligible toddlers, with parental consent, will be assigned to the two study groups in a 1:1 ratio using  
52 the minimization method with the following stratification factors: the centre, the children's age, level  
53 of language (according to the ADOS2 scale) and gender. To ensure allocation concealment, a  
54 minimization algorithm with a .90 random element will be used and known only to the statistician  
55 (AD). The randomisation will be centralized.  
56  
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## ***Blinding***

Owing to the nature of the intervention, parents and PACT therapists cannot be blind to the allocation group. PACT therapists will not be involved in ASD assessment and diagnosis. An assessor blind to the allocation group will administer every assessment. Data manager and biostatistician will be blinded to the allocation groups.

## **Data collection and management**

### ***Data collection***

Data will be collected through standardized observations, parental questionnaires and interviews carried out by a researcher blind to the allocation. We will be particularly vigilant about the measurement accuracy of the first criterion of judgement as described in the paragraph on ADOS-2.

### ***Participation retention and follow-up***

Children of both groups will benefit from early diagnosis and assessment and will have the same follow-up evaluations over the 1-year study period in the respective study centres Any discontinuation of study participation will be collected and recorded with the reasons.

### ***Data Management***

The study data will be collected on a secure electronic case report form (eCRF) that will be available at each centre through an internet portal. No personal identifying information will be mentioned on the eCRF. Each subject included in the study will be assigned a unique identification number.

All study data will be stored securely in the Academic Hospital of Lyon. All electronic data will be secured on a password-protected laptop. Paper-based study documents will be stored in a secure filing cabinet at each centre. Access to these files will be limited to research staff involved in the study.

The eCRF will only include the data necessary for the analysis to be reported in a scientific publication.

## **Statistical analysis**

### ***Simple size calculation***

On the basis of the findings of the PACT Trial (Green, 2010), we have powered the study to be able to detect a difference in overall change on the ADOS score of 2 points. The group difference in mean change between baseline and month 12 was -1 point for ADOS social affect score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group) and -0.5 points for ADOS restricted and repetitive behaviors score (mean change=2.9, SD=3.9 in TAU group and mean change=-3.9, SD=4.7 in PACT+TAU group). The pre- and post-measures were correlated at 0.67. Therefore, the most conservative values were fixed for ADOS standard deviation and for correlation among the repeated measures from a single participant. A target of 238 subjects (119 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 2-point difference in favor of the PACT+TAU compared with TAU, a standard deviation of 5, a correlation between subsequent visits of 0.5, a drop-

1  
2  
3 out rate of 20%, and a two-sided significance level of 0.05, the planned sample size would provide  
4 about 80% power for the study.  
5  
6  
7

### 8 ***Feasibility of recruitment***

9  
10 A strong partnership with ASD orientation platforms recently implemented in France, a broad  
11 communication (meeting, mail, flyers) to healthcare professionals (Speech pathologist, Occupational  
12 therapist, therapist, paediatrician, general practitioner) family associations and other stakeholders will  
13 allow the trial team to reach the sample size within two years.  
14  
15  
16

### 17 ***Statistical analysis***

18  
19 A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will  
20 be reported at the 12-month endpoint in accordance with the CONSORT 2010 statement. No interim  
21 analysis will be scheduled. All the statistical analysis will be carried out according the intention to treat  
22 principle using SAS statistical software (SAS Institute Inc., Cary, NC, USA).  
23  
24  
25

26  
27 Baseline characteristics will be presented in each group.  
28

29 Summary statistics will be presented for process variables (number of PACT sessions, quality of  
30 videoconferencing per session, acceptability and satisfaction of PACT intervention, number of hours  
31 declared to be realized with the child) to show the feasibility and acceptability of PACT implementation  
32 in the intervention group.  
33  
34

35 The pattern of missing data will be investigated (number and mechanism of missingness). Missing data  
36 strategies can be applied, and sensitivity analysis of different strategies (simple or multiple imputation)  
37 will be conducted.  
38  
39

40 A repeated measures analyses will be used to test the effect of PACT intervention on overall ADOS  
41 module 1 score over the 12-month study period. A linear mixed model will be run with the overall  
42 ADOS score as the dependent variable and including time (baseline, month 12), treatment (TAU or  
43 TAU+PACT) and the interaction between treatment and time as fixed effects and patient as random  
44 effect. Model will be adjusted for stratification factors (centre, age, level of language (item A1 ADOS-  
45 2) and gender) and baseline variables that show evidence of treatment group imbalance. Time will be  
46 represented by dummy variable. Model assumption will be verified according to residual analysis. If  
47 most of the assumptions are not met, other alternatives such as transformation of ADOS overall raw  
48 score will be examined. Sensitivity analyses like complete case and per-protocol analysis will be  
49 performed to assess the robustness of the results to protocol deviations. In complete case analysis,  
50 only patient with primary outcome documented will be analyzed. In per-protocol participants who  
51 violate the protocol will be excluded from the analysis.  
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56 All the secondary outcomes, (overall total score of the BOSCC, communication initiation and synchrony  
57 measured with the DCMA, overall raw score of the MSEL in receptive and expressive language, overall  
58 score in expressive language of the DLFP, overall raw score of communicative and social of the VABS,  
59 Parental Stress Index, Parent General Health score, AFEQ score) will be analyzed in a similar way using  
60

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3 with appropriate linear or generalized linear mixed models. Tobit models will be used to address  
4 potential floor effects.  
5

6 We will finally explore the parent's and children's characteristics, moderating the implementation and  
7 efficacy of this therapy. We will also test the previously described mediators implicated in the efficacy  
8 of this therapy [14].  
9

### 10 **Qualitative analysis of barriers and facilitators of implementation**

11  
12 Based on parents and of the therapist's reports, we will describe the facilitators and barriers of the  
13 implementation of video-conferencing PACT.  
14

15  
16 The data will be collected through semi-structured interview and will be analysed with the classical  
17 technique of Interpretative Phenomenological Analysis (IPA) [36]. Population selection will follow the  
18 rules of the purposive sampling and will allow a maximal variation of the sample [37]. An estimation  
19 of 30-60 parents will be necessary to reach data saturation based on previous studies [38-40]. The  
20 total number of therapists (around 7-8) will be interviewed. During the 40-60 minutes interview, we  
21 will explore the barriers and facilitators to implementing PACT by videoconferencing. A guide for the  
22 interview will be elaborated in the initial phase of the project based on first interviews. Interviews will  
23 be recorded and transcribed before analyses.  
24  
25

26  
27 Data from the quantitative and qualitative sources in the process evaluation will be analysed  
28 separately. The results of the qualitative study will be integrated with the quantitative results to  
29 optimize the findings [41].  
30  
31

### 32 **Monitoring**

33  
34 Dr Marie-Maude Geoffray (IP) Investigators associated, methodologists, statistician, parent  
35 representatives and associate researcher composed the trial steering committee (TSC). The TSC is  
36 independent of sponsor and funders and have no competing interests. The TSC has developed the  
37 study protocol and is responsible for data collection, management, publications and the final data  
38 set.  
39  
40

41  
42 The coordinating center is independent from the centers for investigation.  
43

44  
45 According to the French law, the study requires formal data monitoring undertaken by the sponsor.  
46 Annual reporting will be completed and submitted to the funders.  
47

### 48 **Adverse events**

49  
50 Based on results from previous PACT intervention trials, no specific harm from trial participation is  
51 anticipated. However, as required by the French law, adverse events will be collected throughout the  
52 study and reported in the eCRF section. Description of the event, date of occurrence, intensity,  
53 severity, accountability will be reported. Outcomes of this event and action taken after its report will  
54 also be concealed.  
55  
56

57  
58 We anticipate that the early assessment, follow-up consultation on ASD and its management will help  
59 and support both groups during the post-diagnosis period. Hence, no post-trial care is planned.  
60

### **Trial status**

The trial status is currently Recruiting. The study has started the 30th June 30, 2020. The anticipated end date will be 30th June 2023.

Figure 3 shows WHO trial registration data set. Figure 4 shows SPIRIT Checklist.

**Ethics and Dissemination:** This study (protocol version N°5, date: 10/25/2019) is approved by the French National Review Board (reference No 2018-A02516-49). The results will be disseminated via peer-reviewed journals. It will also disseminate via national and international, general and specialist meeting and through the parent association (<https://Bleunetwork.fr>; <https://autisme-ambitionavenir.com>; [desailespourgrandir.org](https://desailespourgrandir.org)). An individual feedback to the participant will be done through a regular newsletter. We will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors.

**Author contribution:** MMG and ST, PO, LJ conceived and designed the project, and MMG is leading the coordination of the trial. MMG, LJ and PO drafted the protocol and procured the project funding. LJ and MMG are responsible for study implementation, staff training and supervision. PO, ST, AD, AZ contributed to the sample size calculation, the randomisation procedure and the statistical plan, and are responsible for data management, randomisation and statistical analysis. JG contributed to the protocol and paper writing. ARL contributed to the protocol of the qualitative study. CA and NG to the PACT training and supervision of the team. MMG, MJO, LJ, AA, AJ, AB, CS, TM, TD are responsible for recruitment and evaluation of children. SG contributed to draft the paper. All authors critically reviewed and approved the final version of the manuscript.

**IFPAD Study group:** Mrs Pauline Auphan (psychologist), Mrs Laetitia Bouveret (research assistant), Mrs Laurie Herman (research assistant), Dr Anne-Laure Toureille (PACT trainer), Mrs Lucie Jansen (PACT trainer), Dr Sandrine Sonié (CRA Lyon), Pr. Mario Speranza (CHU Versaille), Pr. Bruno Falissard (Paris), Pr Nicolas Georgieff (Lyon), Dr Matias Winter (HCL), Mrs Nadège Alloisio (parent association), Mr Chams-Ddine BELKHAYAT (parent association).

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**Disclaimer:** The funders and sponsor (CH le Vinatier, 95, boulevard Pinel, France) have no role in study design, data collection, management, data analysis and interpretation of data, in the writing of the report or in the decision to submit the manuscript for publication.

**Competing interests' statement:** None declared.

**Consent:** Obtained from both parents of the child (Please find in Appendix 2).

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3 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
4

5 **Data sharing statement:** The trial statisticians will have access to the data set for the analysis of trial  
6 outcomes. The PI will have access to the data and will take full responsibility for the analysis and  
7 publication of the results. Once the main analyses have been undertaken, data will be available to  
8 principal and other investigator subject for approval of data analysis plans by the steering  
9 committee.  
10  
11

### 12 **Figure legends**

13  
14  
15 Figure 1- Consort flow-chart of the study

16  
17 Figure 2- Schedule of enrolment, interventions and assessments (SPIRIT)

18  
19 Figure 3- WHO trial registration data set

20  
21 Figure 4- SPIRIT Checklist  
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### 23 **References**

- 24  
25 1 Kogan MD, Vladutiu CJ, Schieve LA, *et al.* The Prevalence of Parent-Reported Autism  
26 Spectrum Disorder Among US Children. *Pediatrics* 2018;**142**:e20174161. doi:10.1542/peds.2017-  
27 4161  
28  
29 2 Lyall K, Croen L, Daniels J, *et al.* The Changing Epidemiology of Autism Spectrum Disorders.  
30 *Annu Rev Public Health* 2017;**38**:81–102. doi:10.1146/annurev-publhealth-031816-044318  
31  
32 3 Baghdadli A, Miot S, Rattaz C, *et al.* Investigating the natural history and prognostic factors of  
33 ASD in children: the multicentric Longitudinal study of childrEN with ASD-the ELENA study protocol.  
34 *BMJ Open* 2019;**9**:e026286.  
35  
36 4 Howlin P. Living with impairment: The effects on children of having an autistic sibling. *Child:*  
37 *care, health and development* 1988;**14**:395–408.  
38  
39 5 HAS. Trouble du spectre de l'autisme Signes d'alerte, repérage, diagnostic et évaluation chez  
40 l'enfant et l'adolescent. 2018;:45.  
41  
42 6 Geoffroy M-M, Thevenet M, Georgieff N. News in early intervention in autism. *Psychiatr*  
43 *Danub* 2016;**28**:66–70.  
44  
45 7 Oono IP, Honey EJ, McConachie H. Parent-mediated early intervention for young children  
46 with autism spectrum disorders (ASD). *Evidence-Based Child Health: A Cochrane Review Journal*  
47 2013;**8**:2380–479.  
48  
49 8 Zwaigenbaum L, Bauman ML, Choueiri R, *et al.* Early intervention for children with autism  
50 spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics*  
51 2015;**136**:S60–81.  
52  
53 9 French L, Kennedy EMM. Annual Research Review: Early intervention for infants and young  
54 children with, or at-risk of, autism spectrum disorder: a systematic review. *J Child Psychol Psychiatry*  
55  
56  
57  
58  
59  
60



1  
2  
3 2018;**59**:444–56. doi:10.1111/jcpp.12828  
4

5 10 Sandbank M, Bottema-Beutel K, Crowley S, *et al*. Project AIM: Autism intervention meta-  
6 analysis for studies of young children. *Psychological Bulletin* 2020;**146**:1–29. doi:10.1037/bul0000215  
7

8 11 Green J, Garg S. Annual Research Review: The state of autism intervention science: progress,  
9 target psychological and biological mechanisms and future prospects. *Journal of Child Psychology and*  
10 *Psychiatry* 2018;**424**–43. doi:10.1111/jcpp.12892@10.1111/(ISSN)1469-  
11 7610.Jack\_Tizard\_VI\_Autism\_Learning\_Disabilities  
12

13 12 Green J, Charman T, McConachie H, *et al*. Parent-mediated communication-focused  
14 treatment in children with autism (PACT): a randomised controlled trial. *The Lancet* 2010;**375**:2152–  
15 60.  
16

17 13 Pickles A, Le Couteur A, Leadbitter K, *et al*. Parent-mediated social communication therapy  
18 for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet*  
19 2016;**388**:2501–9. doi:10.1016/S0140-6736(16)31229-6  
20

21 14 Pickles A, Harris V, Green J, *et al*. Treatment mechanism in the MRC preschool autism  
22 communication trial: implications for study design and parent-focussed therapy for children. *J Child*  
23 *Psychol Psychiatry* 2015;**56**:162–70. doi:10.1111/jcpp.12291  
24

25 15 Vismara LA, McCormick CEB, Wagner AL, *et al*. Telehealth Parent Training in the Early Start  
26 Denver Model: Results From a Randomized Controlled Study. *Focus Autism Other Dev Disabl*  
27 2018;**33**:67–79. doi:10.1177/1088357616651064  
28

29 16 Vismara LA, McCormick C, Young GS, *et al*. Preliminary Findings of a Telehealth Approach to  
30 Parent Training in Autism. *J Autism Dev Disord* 2013;**43**:2953–69. doi:10.1007/s10803-013-1841-8  
31

32 17 Green J, Aldred C, Charman T, *et al*. Paediatric Autism Communication Therapy-Generalised  
33 (PACT-G) against treatment as usual for reducing symptom severity in young children with autism  
34 spectrum disorder: study protocol for a randomised controlled trial. *Trials* 2018;**19**:514.  
35 doi:10.1186/s13063-018-2881-3  
36

37 18 Khan K, Hall CL, Davies EB, *et al*. The Effectiveness of Web-Based Interventions Delivered to  
38 Children and Young People With Neurodevelopmental Disorders: Systematic Review and Meta-  
39 Analysis. *J Med Internet Res* 2019;**21**:e13478. doi:10.2196/13478  
40

41 19 Bearss K, Burrell TL, Challa SA, *et al*. Feasibility of Parent Training via Telehealth for Children  
42 with Autism Spectrum Disorder and Disruptive Behavior: A Demonstration Pilot. *J Autism Dev Disord*  
43 2018;**48**:1020–30. doi:10.1007/s10803-017-3363-2  
44

45 20 Richards DA, Bazeley P, Borglin G, *et al*. Integrating quantitative and qualitative data and  
46 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
47 doi:10.1136/bmjopen-2019-032081  
48

49 21 Fetters MD, Curry LA, Creswell JW. Achieving Integration in Mixed Methods Designs-  
50 Principles and Practices. *Health Serv Res* 2013;**48**:2134–56. doi:10.1111/1475-6773.12117  
51

52 22 Kim SH, Thurm A, Shumway S, *et al*. Multisite Study of New Autism Diagnostic Interview-  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 Revised (ADI-R) Algorithms for Toddlers and Young Preschoolers. *J Autism Dev Disord* 2013;**43**:1527–  
4 38. doi:10.1007/s10803-012-1696-4  
5  
6 23 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.  
7  
8 24 Aldred C, Green J, Emsley R, *et al*. Brief report: Mediation of treatment effect in a  
9 communication intervention for pre-school children with autism. *Journal of autism and*  
10 *developmental disorders* 2012;**42**:447–54.  
11  
12 25 Dunn G, Emsley R, Liu H, *et al*. Evaluation and validation of social and psychological markers  
13 in randomised trials of complex interventions in mental health: a methodological research  
14 programme. *Health Technology Assessment* 2015;**19**. doi:10.3310/hta19930  
15  
16 26 Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism  
17 spectrum disorders. *Journal of autism and developmental disorders* 2009;**39**:693–705.  
18  
19 27 Lord C, Risi S, Lambrecht L, *et al*. The autism diagnostic observation schedule-generic: a  
20 standard measure of social and communication deficits associated with the spectrum of autism. *J*  
21 *Autism Dev Disord* 2000;**30**:205–23.  
22  
23 28 McConachie H, Parr JR, Glod M, *et al*. Systematic review of tools to measure outcomes for  
24 young children with autism spectrum disorder. *Health Technology Assessment* 2015;**19**:1–506.  
25 doi:10.3310/hta19410  
26  
27 29 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th*  
28 *ed.)*. Washington, DC. 2013.  
29  
30 30 Grzadzinski R, Carr T, Colombi C, *et al*. Measuring Changes in Social Communication  
31 Behaviors: Preliminary Development of the Brief Observation of Social Communication Change  
32 (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9  
33  
34 31 Bassano D, Labrell F, Bonnet P. Le Développement du langage de production en français  
35 (DLPF) entre 18 et 42 mois : une synthèse. *Enfance* 2020;**N°2**:151. doi:10.3917/enf2.202.0151  
36  
37 32 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS Pearson  
38 2005.  
39  
40 33 Leadbitter K, Aldred C, McConachie H, *et al*. The Autism Family Experience Questionnaire  
41 (AFEQ): An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life and  
42 Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62.  
43 doi:10.1007/s10803-017-3350-7  
44  
45 34 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire :  
46 validation et normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier  
47 et Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar  
48  
49 35 Pariente P, Challita H, Mesbah M, *et al*. The GHQ-28 questionnaire in French : a validation  
50 survey in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.  
51  
52 36 Smith JA, Shinebourne P. Interpretative phenomenological analysis. In: Cooper H, Camic PM,  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Long DL, *et al.*, eds. *APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological*. Washington: : American Psychological Association 2012. 73–82. doi:10.1037/13620-005

7  
8 37 Guba EG, Lincoln. *Fourth generation evaluation*. Sage Publications, Inc. 1989.

9  
10 38 Lachal J, Speranza M, Taïeb O, *et al.* Qualitative research using photo-elicitation to explore  
11 the role of food in family relationships among obese adolescents. *Appetite* 2012;**58**:1099–105.  
12 doi:10.1016/j.appet.2012.02.045

13  
14 39 Gorse P, Nordon C, Rouillon F, *et al.* Subjective Motives for Requesting In-Patient Treatment  
15 in Female with Anorexia Nervosa: A Qualitative Study. *PLoS ONE* 2013;**8**:e77757.  
16 doi:10.1371/journal.pone.0077757

17  
18 40 Morse JM. The Significance of Saturation. *Qual Health Res* 1995;**5**:147–9.  
19 doi:10.1177/104973239500500201

20  
21 41 Richards DA, Bazeley P, Borglin G, *et al.* Integrating quantitative and qualitative data and  
22 findings when undertaking randomised controlled trials. *BMJ Open* 2019;**9**:e032081.  
23 doi:10.1136/bmjopen-2019-032081  
24  
25  
26  
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28  
29  
30  
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Figure 1 Consort flow-chart of the study.

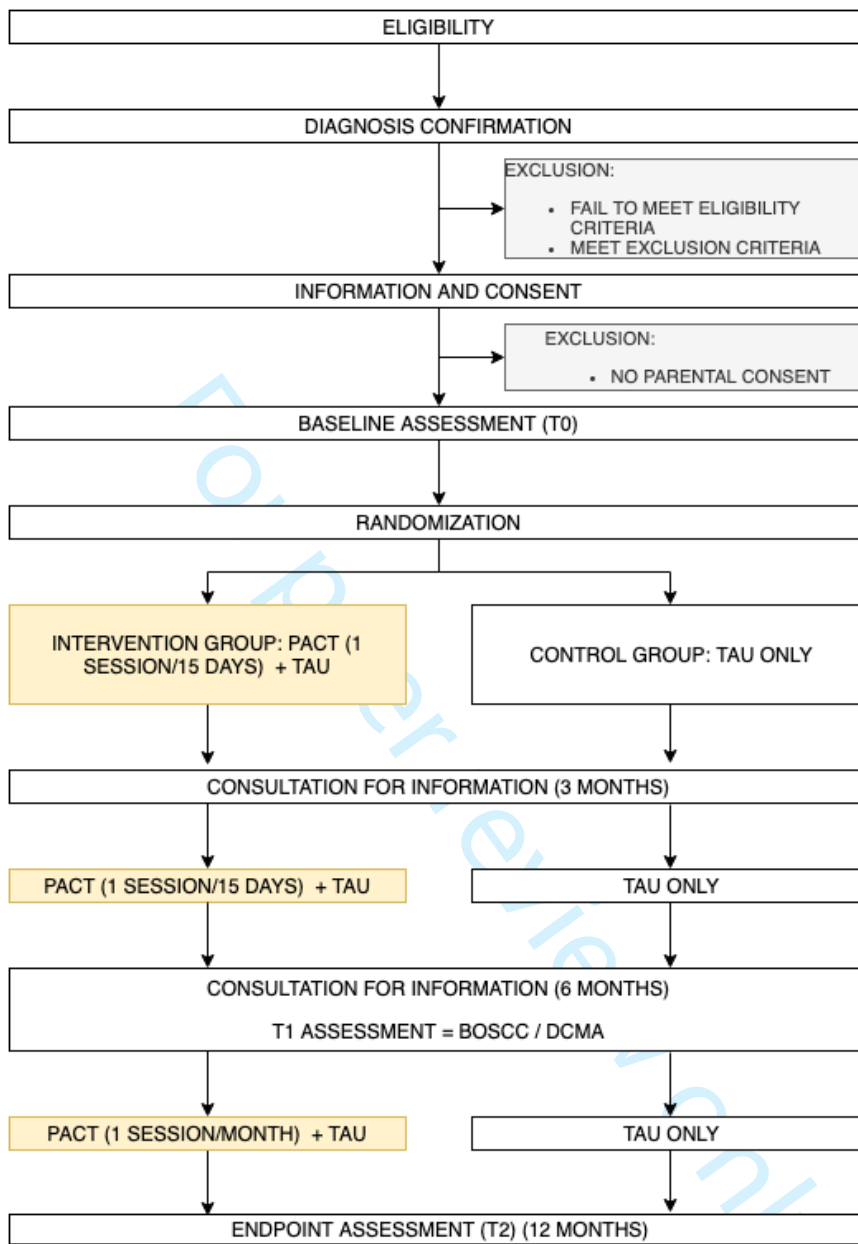


Figure 2. Schedule of enrolment, interventions and assessments (SPIRIT)

Time point	Enrolment	T0 baseline	T1 6 months	T2 12 months
<b>Eligibility screen</b>				
DSM-5 criteria	x			
ADOS-2	x			
ADI-R for toddlers	x			
Nonverbal skills MSEL	x			
Adaptative behavioral level : VABS 2 coded based on an interview done by videoconferencing with parents	x			
Informed consent	x			
Allocation		x		
<b>Intervention</b>				
PACT training (1h/15 days during 6 months then 1h/month during 6 months) + daily practice at home			—————→	
Treatment as usual			—————→	
<b>Assessment</b>				
Sociodemographic data		x		x
Autistic symptoms: ADOS-2 (primary outcome)		x		x
Change in socio-communicative interactions: BOSCC Played-based interaction between carer and child at home		x	x	x
Communication Synchronization and initiatives: DCMA at home		x	x	x
Expressive and receptive language Mullen scale		x		x
Daily language DLFP		x		x
Adaptative behavioral level: VABS 2 by video-conferencing		x		x
Parental stress index: ISP-short form		x		x
General parents health : GHQ-28		x		x
Parents quality of life and priorities. AFEQ		x		x
Acceptability of PACT intervention and TAU. (Linkert scale)				x
<b>Implementation:</b>				
Number of PACT training session				x
Mean of quality of videoconferencing collected after each session				x
Number of hours declared by parents using PACT at home				x

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov : NCT04244721
Date of registration in primary registry	January 28, 2020
Secondary identifying numbers	2018-A02516-49
Source of monetary or material support	This study is supported by a grant from the Programme Hospitalier de Recherche Clinique inter-régional Rhône Alpes (PHRCI-15-065) from the AURA region and a grant by the Caisse Nationale de solidarité pour l'autonomie (CNSA) as part of the call for projects launched for IReSP (Institut de Recherche en Santé Publique) in 2016 in collaboration with the Institut national de la santé et de la recherche médicale (Inserm) ( IReSP-17-Autisme3-16).
Primary sponsor	Centre Hospitalier Le Vinatier, Bron, France
Secondary sponsor	Not applicable
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Public title	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Scientific tittle	Efficacy of a parent- mediated communication-focused treatment in toddler with autism (PACT)when parents trained by videoconference: a randomised controlled trial study protocol
Countries of recrutement	France
Health condition or problem studied	Autism spectrum disorder (ASD)
Interventions	<i>Intervention:</i> PACT for toddlers and young children with ASD <i>Description:</i> PACT delivered by the parent trained remotely by therapists 1 hour per 2-weeks during 6 months and 1 hour per month the following 6 months. <i>Control:</i> care available in the community, i. e. consultations with a psychologist or child and adolescent psychiatrist, speech and language therapy, occupational therapy, individual or group psychotherapy.
Key inclusion and exclusion criteria	<i>Age:</i> between 18 and 36 months <i>Sex:</i> male or female <i>Inclusion criteria:</i> diagnosis of ASD (Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, and Autism Diagnosis Observation Schedule), child will have a non-verbal age above 12 months on the Mullen Scale of Early learning, family living further than 40 min away from an ASD specialized center. <i>Exclusion criteria:</i> serious neurological or physical condition, family unavailable for a regular follow-up.
Study type	Interventional <i>Allocation:</i> randomized 1:1; parallel assignment; blinding: assessor blind
Date of first enrolment	15th July 2020
Target sample size	238
Recrutment status	Recruiting
Primary outcome	Change in ADOS-2 module 1 standardized score at 12 months
Key secondary outcomes	Child development, child adaptative behavior, child socio-communicative abilities, quality of life of parents, parental stress, obstacle and facilitators of the intervention model.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	12 (fig 3)
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4



## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9 (fig 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

## Methods: Assignment of interventions (for controlled trials)

### Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	10
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13				
14				
15		17b	If blinded, circumstances under which unblinding is permissible, and	10
16			procedure for revealing a participant's allocated intervention during	
17			the trial	
18				
19				
20	<b>Methods: Data collection, management, and analysis</b>			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	10
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27				
28				
29				
30		18b	Plans to promote participant retention and complete follow-up,	10
31			including list of any outcome data to be collected for participants who	
32			discontinue or deviate from intervention protocols	
33				
34	Data	19	Plans for data entry, coding, security, and storage, including any	10
35	management		related processes to promote data quality (eg, double data entry;	
36			range checks for data values). Reference to where details of data	
37			management procedures can be found, if not in the protocol	
38				
39				
40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	11
41	methods		Reference to where other details of the statistical analysis plan can be	
42			found, if not in the protocol	
43				
44				
45		20b	Methods for any additional analyses (eg, subgroup and adjusted	11
46			analyses)	
47				
48		20c	Definition of analysis population relating to protocol non-adherence	11
49			(eg, as randomised analysis), and any statistical methods to handle	
50			missing data (eg, multiple imputation)	
51				
52	<b>Methods: Monitoring</b>			
53				
54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	12
55			and reporting structure; statement of whether it is independent from	
56			the sponsor and competing interests; and reference to where further	
57			details about its charter can be found, if not in the protocol.	
58			Alternatively, an explanation of why a DMC is not needed	
59				
60				

1				
2		21b	Description of any interim analyses and stopping guidelines, including	12
3			who will have access to these interim results and make the final	
4			decision to terminate the trial	
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and	12
7			spontaneously reported adverse events and other unintended effects	
8			of trial interventions or trial conduct	
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and	13
12			whether the process will be independent from investigators and the	
13			sponsor	
14				
15				
16	<b>Ethics and dissemination</b>			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board	13
18	approval		(REC/IRB) approval	
19				
20	Protocol	25	Plans for communicating important protocol modifications (eg,	13
21	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties	
22			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
23			regulators)	
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial	13
27			participants or authorised surrogates, and how (see Item 32)	
28				
29		26b	Additional consent provisions for collection and use of participant data	NA
30			and biological specimens in ancillary studies, if applicable	
31				
32				
33	Confidentiality	27	How personal information about potential and enrolled participants will	13
34			be collected, shared, and maintained in order to protect confidentiality	
35			before, during, and after the trial	
36				
37	Declaration of	28	Financial and other competing interests for principal investigators for	13
38	interests		the overall trial and each study site	
39				
40				
41	Access to data	29	Statement of who will have access to the final trial dataset, and	14
42			disclosure of contractual agreements that limit such access for	
43			investigators	
44				
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	12
46	post-trial care		compensation to those who suffer harm from trial participation	
47				
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	13
49	policy		participants, healthcare professionals, the public, and other relevant	
50			groups (eg, via publication, reporting in results databases, or other	
51			data sharing arrangements), including any publication restrictions	
52				
53				
54		31b	Authorship eligibility guidelines and any intended use of professional	13
55			writers	
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-	14
58			level dataset, and statistical code	
59				
60				

## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	App 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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## Appendix 1: Secondary outcomes

The secondary outcomes are measured using standardized coding assessments of naturalistic observational videos (BOSCC, DCMA), performance-based standardized tests (MSEL), and parent-report-based standardized tests (VABS, DLFP, AFEQ, ISP, GHQ).

### To assess social communication and interaction in the natural setting of parent-child interaction at home

*Brief Observation of Social Communication Change (BOSCC)* measures the same construct as the ADOS. It is a researcher coding assessment of autism symptoms based on child-adult interaction. It has good fidelity and results showed good construct validity [1]. The validity to measure the change was analysed in two small populations (N=20-50) and will have to be reanalysed in further trials [36,37]. It has the advantage to allow measure Dyadic interaction across different contexts. It was translated and retro-translated for the purpose of a previous study [2]

The scale is composed of 12 items scored from 0 to 5 according to the BOSCC algorithm. There is an overall score of 0 to 60 measuring core autism symptoms. A higher score indicates more autistic symptoms.

In the current study, a 12 minutes home-video will be recorded by the parents themselves. The parent will be provided with a simple protocol to follow using a standardized set of toys. The standardized set of toys given to the families at each time of assessment will include a cause and effect toy, shape sorter or puzzle, construction toys, miniature pretend play. The protocol includes 10 minutes time of natural play with children with the set of standardized toys and 2 minutes with bubbles play. A first unscored videotape would be done on the center (at T0) to train the parents to video record based on the protocol. In the week following, the parent will videotape at home a child-parent interaction according to the protocol with the standardized set of toys and send the video to the researchers via a secure platform. Professional may make up to two further requests if the video received is judged to not be of adequate quality. If the parent isn't able to send a usable video according to the protocol, the researcher completes a home visit to demonstrate and help the parent to do the video the third time. Two further videos will be done at home at 6 months (T1) and 12 months (T2) in order to assess Social communication interaction in a naturalistic setting.

All the video will be scored by trained researchers.

The same parent called the "referent parent" will be videotaped by a relative at each time of assessment. He/ she will be identified before the randomisation. It will also be the parent who receive PACT therapy if in the group of PACT intervention.

### To assess dyadic communication in the natural setting of parent-child interaction at home

The *Dyadic Communication Measure for Autism (DCMA)* is a direct observation instrument of the communication between a parent and a child with autism [3]. It rates parental and child mutual shared attention, child communication (initiation and response) and parental communication style (synchronous/asynchronous).

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2  
3 Independent inter-rated reliability on synchrony has been reported and is good [3]. It was translated  
4 and retro-translated for the purpose of a previous study [2]

5  
6 It can be used to code a number of acts of communication per timepoint. A higher score indicates  
7 better communication.  
8

9  
10 Coding will be done on the same 12 minutes home parent-child video described above in BOSCC at  
11 baseline, 6 months and 12 months.  
12

### 13 **To assess child cognitive development**

14  
15 The *Mullen Scales of Early Learning (MSEL)* is a direct observation standardized tool from birth to 68  
16 months [4]. It measures verbal and non-verbal skills of the children, according to the success or failure  
17 in tasks of the MSEL protocol delivered by a trained researcher. The MSEL has been used extensively  
18 as a discriminative and evaluative measure in children with autism spectrum disorder, Fragile X  
19 syndrome, and speech delays [5–7]  
20

21  
22 The MSEL will be assessed on the center before the inclusion and at 12 months.  
23

24  
25 Internal consistency and concurrent validity are good [4]. It was translated and retro-translated for  
26 the purpose of a previous study [2]  
27

28  
29 The MSEL includes 124 items that measure five specific domains: 1) Gross Motor; 2) Fine  
30 Motor; 3) Visual Reception; 4) Expressive Language; and 5) Receptive Language. Scoring varies  
31 by item from 2-point scale (0 = does not meet criteria to 1 = meets criteria) to a 6-point scale. Results  
32 for each scale are described by T scores (M = 50, SD = 10), percentile ranks, and age equivalents.  
33 Four cognitive scales (Visual Reception, Fine Motor, Receptive Language, and Expressive  
34 Language) sum to represent an Early Learning Composite Score which measures overall  
35 cognitive functioning (M=100, SD=15). A higher score means better skills. This evaluation will be  
36 realized before inclusion and at 12 months.  
37

### 38 39 **To assess child language development**

40  
41 The “development of expressive language”, a standardised French Scale (Development du Language  
42 de Production In french\_DLPF), is based on a self-administered parent-report [8]. This measure is  
43 standardised for age. Only the level 4 of the DLFP will be administered at each assessment to have a  
44 continuous score on expressive language. The DLFP was validated in a study [3]. Score is calculated  
45 based on the number of words in the naturalistic environment of the child as reported by the parents.  
46 A higher score means better language skills. This questionnaire will be completed by the referent  
47 parent at baseline and at 12 months.  
48

49  
50 It will complete the measure of functional communication with VABS-2 and standardised measure with  
51 MSEL.  
52

### 53 54 **Adaptative behavior**

55  
56 Vineland Adaptive Behaviors Scales second version (VABS-2) is a parent reported scale to measure the  
57 child’s daily personal and social skills [9]. This measure will be collected via a parental interview over  
58 videoconferencing before the inclusion and at 12 months. Videoconferencing model has been chosen  
59  
60

1  
2  
3 in our study to avoid multiples visits on the centre but also to evaluate, before the inclusion, if a long  
4 videoconferencing meeting could be done with the family on a technical point of view. A first  
5 assessment will be proposed to the parents. In case of technical difficulties during the first meeting, a  
6 second, and if necessary, a third meeting will be proposed. Tips to improve videoconferencing will also  
7 be provided to the parents. In case of failure of every remote assessment, the family will be considered  
8 as not eligible for the study as the remote PACT session require the ability to conduct a  
9 videoconferencing meeting.  
10  
11

12  
13 This measure will provide an estimate of any assesses functional change in socialization,  
14 communication, motor and daily living skills, based on parent observation in the naturalistic settings  
15 of the child.  
16

17  
18 The VABS has well-established psychometric properties [9,10]. It is validated in french.  
19

20  
21 All of the items are rated on a three-point Likert scale, ranging from '0' (seldom or never present) to  
22 '2' (always present). Results for each scale are described by t scores (M = 50, SD = 10). An overall score  
23 is described by normalized score (M=100, SD=15). The range for each subscale is from 20 to 140. The  
24 subscales are summed to compute a total score, ranging from 80 to 560. The higher the scores are, the  
25 better adaptive functioning the children achieve.  
26

### 27 28 **To assess Parent's Stress, health, priorities and experience of the family**

29  
30 The psychometry of the following tools are described in the manual of each tool.  
31

32  
33 *Autism Family Experience (AFEQ)* [11] is a 48-item self-administered parent report about quality of life  
34 and priorities for early intervention. It is composed of 4 subscales: experience of being a parent (range  
35 13-65), family life (range 9-45), child development understanding and relationships (14-70), child  
36 symptoms (12-60). The sum of all domains gives the total score (range 48 - 240). Each question is  
37 assessed using a 5-point Likert scale. Scores range from "always" (1) to "never" (5)". It was translated  
38 and retro-translated for the purpose of this study with the author. For the total score and the domain  
39 scores a higher score indicates a lower outcome. This questionnaire will be completed by the referent  
40 parent at baseline and at 12 months.  
41  
42

43  
44 *ISP (Parental stress index)* is a 36-item self-administered parent report to measure the stress in the  
45 parent-child system. The PSI consists of three subscales: Parental Distress, Parent-child Dysfunction  
46 Interaction, and Difficult Child. Each subscale consists of 12 items rated from 1 (strongly agree) to 5  
47 (strongly disagree), with subscale scores ranging from 12 to 60. The three domains combined form a  
48 Total Stress score (with a total score ranges from 36 to 180). We will use the short form of the 4th  
49 edition. A validated French version exists [12]. A higher score on the subscales and total stress score  
50 indicates increased levels of stress. This questionnaire will be completed by the referent parent at  
51 baseline and at 12 months.  
52  
53

54  
55 *General Health Questionnaire (GHQ-28)* is a self-administered parent report, 28 item scaled version,  
56 assessing somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. Each  
57 item is rated according to a Likert score method (1 to 4). The GHQ-28 global score range from 36 to  
58 110 [13]. A higher score means more health problems. This questionnaire will be completed by the  
59 referent parent at baseline and at 12 months.  
60



## To assess implementation of the intervention

### *Professional adherence to the treatment:*

All therapy training sessions with professionals will be videotaped and will be independently rated by the lead therapist using the PACT Fidelity Rating Scale (of the PACT manual) at regular intervals across the trial period. The PACT Fidelity Rating Scale measures how the therapists follow the PACT manual including the style of training.

### *Acceptability and feasibility of the PACT session*

The therapist will collect the number of the session done with each parent. The quality of videoconferencing during each session with the professional will be rated. Quality of sound and quality of the image will be rated with a 4-points Likert scale. The number of disconnections along the session will also be collected.

The parents will self-report (likert-scale) the acceptability of videoconferencing training and implementation of PACT at home.

### *Parent PACT adherence at home*

At 12 months, Parents will declare the average number of hours per day using PACT at home outside the PACT session with the therapist.

DCMA, coded on the 12 minutes home child-parent interaction will measure the parent's qualitative adherence of PACT intervention.

- 1 Grzadzinski R, Carr T, Colombi C, *et al.* Measuring Changes in Social Communication Behaviors: Preliminary Development of the Brief Observation of Social Communication Change (BOSCC). *J Autism Dev Disord* 2016;**46**:2464–79. doi:10.1007/s10803-016-2782-9
- 2 Touzet S, Ocelli P, Schröder C, *et al.* Impact of the Early Start Denver Model on the cognitive level of children with autism spectrum disorder: study protocol for a randomised controlled trial using a two-stage Zelen design. *BMJ open* 2017;**7**:e014730.
- 3 Aldred C, Green J, Emsley R, *et al.* Brief report: Mediation of treatment effect in a communication intervention for pre-school children with autism. *Journal of autism and developmental disorders* 2012;**42**:447–454.
- 4 Mullen EM. *Mullen scales of early learning*. AGS Circle Pines, MN 1995.
- 5 Burns TG, King TZ, Spencer KS. Mullen Scales of Early Learning: The Utility in Assessing Children Diagnosed With Autism Spectrum Disorders, Cerebral Palsy, and Epilepsy. *Applied Neuropsychology: Child* 2013;**2**:33–42. doi:10.1080/21622965.2012.682852
- 6 Bishop SL, Guthrie W, Coffing M, *et al.* Convergent validity of the Mullen Scales of Early Learning and the differential ability scales in children with autism spectrum disorders. *American journal on intellectual and developmental disabilities* 2011;**116**:331–343.
- 7 Farmer C, Golden C, Thurm A. Concurrent validity of the differential ability scales, second edition with the Mullen Scales of Early Learning in young children with and without neurodevelopmental disorders. *Child Neuropsychology* 2016;**22**:556–69. doi:10.1080/09297049.2015.1020775

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3 8 Bassano D, Labrell F, Champaud C, *et al.* Le DLPPF : un nouvel outil pour l'évaluation du  
4 développement du langage de production en français. *Enfance* 2005;**57**:171.  
5 doi:10.3917/enf.572.0171  
6  
7 9 Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales:(VABS)*. NCS Pearson 2005.  
8  
9 10 Chatham CH, Taylor KI, Charman T, *et al.* Adaptive behavior in autism: Minimal clinically important  
10 differences on the Vineland-II: Adaptive behavior and autism. *Autism Research* 2018;**11**:270–83.  
11 doi:10.1002/aur.1874  
12  
13 11 Leadbitter K, Aldred C, McConachie H, *et al.* The Autism Family Experience Questionnaire (AFEQ):  
14 An Ecologically-Valid, Parent-Nominated Measure of Family Experience, Quality of Life and  
15 Prioritised Outcomes for Early Intervention. *J Autism Dev Disord* 2018;**48**:1052–62.  
16 doi:10.1007/s10803-017-3350-7  
17  
18 12 Lacharité C, Éthier L. « Le stress parental chez les mères d'enfants d'âge préscolaire : validation et  
19 normes québécoises pour l'Inventaire de Stress Parental » Carl Lacharité, Louise Éthier et  
20 Christiane Piché. 2013;**17**:183–203. doi:10.7202/502077ar  
21  
22 13 Pariente P, Challita H, Mesbah M, *et al.* The GHQ-28 questionnaire in French : a validation survey  
23 in a panel of 158 general psychiatric patients. *European Psychiatry* 1992;**7**:15–20.  
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Code promoteur : IFPAD

### Formulaire de recueil de consentement de participation à une recherche

**Titre : Efficacité sur la sévérité des signes autistiques du jeune enfant avec un trouble du spectre autistique d'une intervention développementale conduite par les parents formés par visioconférence (IFPAD).**

**Investigateur coordonnateur : Dr Marie-Maude GEOFFRAY**

**Promoteur : CH Le Vinatier**

95 Boulevard Pinel  
69677 BRON CEDEX

Je soussigné représentant légal n°1 : NOM et Prénom : \_\_\_\_\_ Je  
soussigné représentant légal n°2 : NOM et Prénom : \_\_\_\_\_

De l'enfant : NOM et prénom du mineur : \_\_\_\_\_  
Né(e) le :    /    /    à (ville et code postal) : \_\_\_\_\_  
Demeurant : \_\_\_\_\_

Déclare : que le Dr \_\_\_\_\_, nous a proposé de faire participer notre enfant à l'étude sus nommée,

-qu'il nous a expliqué en détail le protocole,

-qu'il nous a notamment fait connaître :

- L'objectif, la méthode et la durée de l'étude
- Les contraintes et les risques potentiels encourus
- mon droit de refuser de participer et en cas de désaccord de retirer mon consentement à tout moment
- notre obligation d'inscription à un régime de sécurité sociale pour mon enfant
- que, si nous le souhaitons, à son terme, nous serons informés par le médecin investigateur de ses résultats globaux
- que le comité de Protection des Personnes Sud-est III a émis un avis favorable en date du 30/10/2018 et a accepté l'amendement de la version N° 5 du protocole en date du 25 octobre 2019.
- que l'ANSM a été informée de la mise en place de cette étude
- que dans le cadre de cette étude le promoteur, le CH le Vinatier, a souscrit à une assurance couvrant cette recherche : Assurance SHAM, 18 rue Edouard Rochet, 69372 LYON CEDEX 08

-que nous avons répondu en toute bonne foi aux questions concernant l'état de santé de notre enfant et sa participation à d'autres études.

Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement. J'accepte que les données enregistrées au cours de l'étude puissent faire l'objet d'un traitement informatisé conformément à la méthodologie MR001 de la Commission Nationale de l'Informatique et des Libertés (CNIL). Nous avons pris connaissance que le Centre Hospitalier Le Vinatier est responsable de nos informations personnelles recueillies dans le cadre de l'étude IFPAD et que ces informations peuvent être conservées pendant 15 ans. Nous avons bien noté que nous disposons d'un droit d'accès et de rectification, d'effacement et d'opposition au traitement des données nous concernant à tout moment de l'étude auprès

Version 5 du 25 octobre 2019

Centre Hospitalier le Vinatier – Service de la Recherche - BP 300 39 – 95 bd Pinel  
69 678 Bron cedex

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du Dr GEOFFRAY, 04.37.91.52.56 ou auprès du responsable de la protection des données du CH Le Vinatier en le contactant à l'adresse mail : [fabien.joubert@ch-le-vinatier.fr](mailto:fabien.joubert@ch-le-vinatier.fr) ou par téléphone au 04.37.91.54.40, dans le respect de la loi « informatique et liberté » (loi du 6 janvier 1978) et du règlement Général à la protection des données (RGPD) entré en vigueur le 25 mai 2018.

Si nous ne sommes pas satisfaits des réponses que nous avons obtenues, nous pouvons nous adresser à la Commission Nationale de l'Informatique et des Libertés (CNIL) en utilisant le lien : <https://www.cnil.fr/>

Nous pouvons également contacter les médecins suivants : Dr GEOFFRAY, 04.37.91.52.56 en cas d'événement indésirable et pour tout renseignement concernant ma participation à l'étude et en cas de problème médical survenu pendant l'étude.

**Après avoir discuté librement et obtenu réponse à toutes nos questions, nous acceptons librement et volontairement de faire participer notre enfant à cette recherche dans les conditions précisées dans le formulaire d'information et de consentement.**

<p>Nom et prénom du représentant légal n° 1 Signature précédée de la mention « <b>lu et compris</b> »</p> <p>Date :    /    / Signature :</p>	<p>Nom de l'investigateur :</p> <p>Date :    /    / Signature :</p>
<p>Nom et prénom du représentant légal n° 2 Signature précédée de la mention « <b>lu et compris</b> »</p> <p>Date :    /    / Signature :</p>	

Document réalisé en 2 exemplaires originaux (dont le premier doit être gardé 15 ans par l'investigateur, et un autre remis aux parents).